Chapter 1

Practical issues in the use of systemic anti-cancer therapy drugs

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Introduction

The role of systemic anti-cancer therapy (SACT) in the management of cancer is evolving rapidly with widening indications for treatment and, in many diagnoses, additional therapies and lines of treatment now available. In 2015, there are now over 140 drugs licensed to be used for cancer treatment and it is not practical within this chapter to give a comprehensive description of each drug or treatment regimen. More detailed information can be found in chemotherapy textbooks, at the manufacturers' websites, the electronic Medicines Compendium (eMC) or from oncology pharmacy websites (e.g. http://www.medicines.org.uk/emc and www.bccancer.bc.ca, accessed January 2015). However, we hope this chapter, which focuses mainly on classic cytotoxic chemotherapy drugs, will provide SACT prescribers, pharmacists and administrators with sufficient information to discuss treatment with patients, to prescribe and deliver drugs safely and to recognise common treatment-related side effects.

Over the last decade there has been a major increase in activity and workloads within chemotherapy treatment units. The 2009 National Cancer Advisory Group report described an increase in overall activity of 60% in just a four year period (NCAG, 2009). This rise in activity is in part a result of increased numbers of patients but there has also been a major expansion in the indications for which there is effective treatment, the upper age range of patients treated and, in many malignancies, the number of lines of therapy available for use. Whilst the newer drugs are predominantly oral agents, the recent development of maintenance monoclonal antibody therapies for breast cancer and non-Hodgkin lymphoma and the more modern prolonged and complex regimens in gastrointestinal malignancies have added considerable pressure to the workload of pharmacy and chemotherapy treatment units.

A summary of the rapid increase in both the number of new cancer treatment drugs and the change in identity of new SACT agents can be see in Table 1.1 that shows both the historical and modern trends in new cancer drugs. This demonstrates the change from the initial cancer treatment drugs of the 1970s/80s/90s that were predominantly classic cytotoxic chemotherapy agents to a new, varied range of agents including monoclonal antibodies, TKI and MTOR inhibitors and other new agents (Savage and Mahmoud, 2013).

This increase in the number and variety of anti-cancer drugs seems set to continue as there are nearly 1000 new cancer drug trials in the USA alone at present (PhRMA, 2012). One of the consequences of the increased numbers of new drugs is the financial challenge in providing the facilities and manpower to deliver care, and to pay for the drugs themselves. This is a problem for all healthcare systems, whether paid by insurance or state-funded, and it is likely that the increasing numbers and cost of cancer drug treatment will continue to influence clinical, economic and political decision making (Sullivan *et al.*, 2011).

Aims of systemic anti-cancer therapy

There are three main indications for the use of SACT drugs.

- Curative: the management of patients with chemotherapy-curable advanced malignancies including gestational choriocarcinoma, testicular cancer, ovarian germ cell tumours, acute leukaemia, Hodgkin lymphoma, high-grade non-Hodgkin lymphoma (NHL) and some rare childhood malignancies.

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Table 1.1 Historical and modern trends in new cancer drugs

Drug class	Pre 1975	1975–1999	2000–2009	2010–13	Total
Cytotoxic	15	30	5	5	55
Hormonal	0	13	3	2	18
Cytokine	0	2	0	0	2
Peptide	0	2	0	1	3
MAb	0	1	5	5	11
TKI	0	0	5	6	11
MTOR	0	0	1	1	2
Other	0	0	3	0	3

The table shows the number of new cancer treatment drugs licensed during each of the time periods and the total currently available in each therapeutic class. MAb = antibody; MTOR: mechanistic target of rapamycin (serine/threonine kinase); TKI: tyrosine kinase inhibitor.

- Adjuvant: the preoperative or postoperative treatment of clinically localised malignancies, primarily breast cancer and colorectal cancer.
- Palliative: the treatment of patients with advanced incurable malignancies, where the main aims of treatment include prolonging life and reducing disease-related symptoms.

Before starting a course of SACT, the prescriber and the patient should both be clear about the aims and realistic expectations of treatment and ideally use consent forms specific to individual regimens and indications giving detailed information on the risks and benefits of treatment.

For patients with curable malignancies or receiving adjuvant therapy, it is important to avoid treatment delays or dose reductions and to maintain the calculated dose and schedule of the standard treatment protocols. The importance of this has been shown in the cure rates for testicular cancer (Toner *et al.*, 2001) and lymphoma (Lepage *et al.*, 1993) and also in the adjuvant treatment of breast cancer, where the rate of relapse is higher when the dose intensity is reduced (Budman *et al.*, 1998).

Generally, the chemotherapy regimens used in the curable malignancies have significant side effects including neutropenia and the use of granulocyte colony stimulating factor (G-CSF) is frequently required to keep treatment on schedule. However because there is the clear intent of achieving either cure or, in adjuvant treatment, an increased chance of cure, these side effects and treatment-related risks and costs are seen as acceptable temporary issues. In contrast, for patients having non-curative chemotherapy the benefits of treatment need to be balanced against quality of life and dose reductions may be made to ensure that the patient tolerates the treatment safely.

Cytotoxic chemotherapy

Cytotoxic chemotherapy drugs aim to kill or slow the growth of tumour cells while being relatively sparing to normal non-malignant cells. The sensitivity of different tumour types to the actions of cytotoxic drugs varies widely among the cells of origin and across the range of drugs. This variation in part reflects native metabolism of the tumour cell and differing metabolic pathways, drug handling, abilities to repair DNA and sensitivity to the induction of apoptosis.

In general tumour cells are more sensitive to cytotoxic drugs than their parent cell types and also often more sensitive than the usually dose limiting cells of the bone marrow. Whilst chemotherapy treatment brings routine cures in the rare chemotherapy curable malignancies, for the common malignancies cure of metastatic disease with chemotherapy is not a realistic outcome. The ability of chemotherapy treatment to cure patients with these limited numbers of chemo curable malignancies, listed above, started in the 1950s and was firmly established by the end of the 1970s. Since then, despite many new classic cytotoxic drugs being subsequently introduced, this pattern of chemotherapy curable malignancies has not changed. Whilst there has been enormous endeavour looking at the mechanisms of chemotherapy resistance, other explanations based on the natural genetic processes occurring in the parent cells of the chemotherapy curable malignancies may offer an alternate perspective (Masters and Köberle 2003, Savage *et al.*, 2009).

The action of cytotoxic chemotherapy drugs has traditionally been classified as being either 'cell-cycle specific' or 'cell-cycle non-specific.' The cycle-specific drugs, (such as the anti-metabolites methotrexate,

fluorouracil and gemcitabine) mainly interact with cells that are actively synthesising DNA in the synthesis (S) phase and so are most effective in tumours with high mitotic rates and kill more cells when given in prolonged exposures.

The cell-cycle non-specific drugs interact with cells in all parts of the cycle and can affect more slowly proliferating tumour cells. These include the alkylating agents (e.g. cyclophosphamide, bendamustine, ifosfamide) and the anti-tumour antibiotics (e.g. bleomycin, doxorubicin, epirubicin). These drugs are active in all phases of the cell cycle, and their effect is more closely related to the total dose rather than to the duration of administration.

More modern research suggests that this distinction is relatively crude and that most drugs affect both dividing and resting cells. However, it is still quite useful for predicting the side effects of chemotherapy, because the extended use of cell-cycle specific drugs can cause more neutropenia and mucosal damage, and for designing combination regimens.

Combination chemotherapy regimens

Most cytotoxic drugs were originally used as single agents and were then incorporated into clinical trials of combination chemotherapy schedules. The combination of drugs with different modes of action and patterns of toxicity led to major improvements in the treatment of testicular cancer and lymphoma and made these tumours routinely curable in the 1970s (Li *et al.*, 1960, Freireich *et al.*, 1964, DeVita *et al.*, 1970). In the adjuvant and palliative setting, combination treatments often also give enhanced results with acceptable toxicity.

The key principles for selecting the chemotherapy drugs for use in combinations include the following.

- Each drug has activity against the tumour as a single agent.
- There are no clinically important drug interactions between the agents.
- Combinations should avoid drugs of the same class or those with similar modes of action.
- The drugs should have different dose-limiting toxicities.

For example, BEP (bleomycin, etoposide, cisplatin) is now the regimen of choice for advanced testicular cancer. The drugs all have significant activity as single agents, usually with a short duration of response, and have different dose-limiting toxicities. By combining them with their different toxicities, each can be used at nearly the full single-agent dose, resulting in increased effectiveness with little extra toxicity. This combination changed advanced testicular cancer from a diagnosis with a poor prognosis to one which was routinely curable (Williams *et al.*, 1987).

The treatment of high-grade B-cell NHL is an example of the benefits of adding an additional modern drug with a completely different mode of action to an already effective regimen. After its introduction in the 1970s the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) became standard treatment (McKelvey *et al.*, 1976), and subsequent trials comparing CHOP with more complex and toxic regimens showed no greater effectiveness (Fisher *et al.*, 1993). In contrast, addition of the anti-CD20 monoclonal antibody rituximab, with a different mode of action and minimal toxicity, to give the R-CHOP regimen has led to significant improvement in cure rates (Sehn *et al.*, 2005).

Chemotherapy scheduling

In some regimens the cytotoxic drugs must be given in the correct order, for example the combination of paclitaxel and carboplatin for patients with ovarian cancer. Carboplatin is a cell-cycle non-specific drug and is best given as a single bolus dose, infused over 30 minutes, because of the risk of hypersensitivity. The usual administration cycle is 28 days when used as a single agent because the myelosuppression nadir is between 14 and 21 days. Paclitaxel is cell-cycle specific and so should be given in multiple fractions over a prolonged period and is now usually given as a 3-hour infusion (ICON Group, 2002). Its nadir of myelosuppression occurs after 10 days, implying a maximum cycle length of 21 days, and so combining the two drugs presents a problem deciding what interval there should be between doses. However, studies have shown that giving paclitaxel before carboplatin appears to give some bone marrow protection and 21-day cycles do not produce unacceptable myelosuppression. However, recent trials giving paclitaxel weekly in combination with 3-weekly carboplatin, a 'dose-dense' schedule, showed greater effectiveness but more toxicity (Katsumata *et al.*, 2013).

SACT protocols and guidelines

The introduction of peer-reviewed treatment policies in the NHS has led to the development of local protocols for approved SACT regimens, which should be

familiar to all the health professionals who prescribe, dispense and administer them. 'Off-protocol' regimens should generally not be prescribed unless there is good evidence in the research literature.

Electronic prescribing systems for SACT have reduced the risk of prescribing errors, improved administration scheduling and provided accurate data on prescribing patterns (Ammenwerth *et al.*, 2008).

Dose calculation

Body surface area

Ideally, calculating the appropriate dose of a cytotoxic drug would take into account its pharmacokinetic properties – how the body delivers the drug to its site of action and the patient's metabolism and excretion. The dose could then be adjusted according to the toxicity seen in each patient. Although this method of chemotherapy drug dosing has been advocated, routine cytotoxic chemotherapy doses continue to be calculated according to the patient's body surface area (BSA) (Veal *et al.*, 2003).

There are several formulae for calculating BSA. The most commonly used is that of DuBois and DuBois, which dates from 1916 and was based on data from only eight adults and one child (DuBois and DuBois, 1916). Other formulae using both electronic and manual methods (nomograms and slide rules) are available, and there is generally good correlation between them.

Dose capping

Whether to dose chemotherapy according to the patient's actual weight or their calculated ideal body weight is controversial (Hall *et al.*, 2013). Using the calculated BSA in large or obese patients may lead to relative overdosing and a risk of increased toxicity. Placing an upper limit on the dose has been suggested and some centres will use 2.2 m^2 as an upper limit of BSA for curative and adjuvant treatments and 2.0 m^2 for palliative treatments. However, when prescribing for tall but non-obese individuals there is a potential risk of underdosing if the BSA is capped at 2.2 m^2. The only commonly agreed exception is in the use of vincristine, for which the dose is usually capped at 2 mg. At present there is no consensus on this, and local policies should always be checked, especially when treating patients with chemotherapy-curable tumours.

Area under the curve dosing

Carboplatin is excreted unchanged by the kidneys and is the only commonly used agent for which the dose is calculated from the renal function. A formula (the Calvert equation) has been developed based on renal function (Calvert *et al.*, 1989) by which the desired AUC (area under the curve of serum levels against time) is chosen, and the dose is calculated by the following formula:

$$\text{Dose (mg)} = \text{desired AUC} \times (\text{GFR mL/min} + 25)$$

GFR is the glomerular filtration rate, which may be calculated by ^{51}Cr-EDTA clearance, using a 24-h urine collection, or from the Cockcroft–Gault equation which derives it from a measure of serum creatinine, weight, age and sex. It is important to know which value of BSA is used in routine reporting of GFR and whether the value relates to the actual body size or to a standardised 1.73 m^2 BSA.

Body weight dosing

Body weight alone is not sufficent for calculating doses of most cytotoxic drugs except for some of the newer drugs, such as trastuzumab.

Flat dosing

Bleomycin is the only commonly used cytotoxic drug for which a fixed dose is used routinely. In the BEP regimen a fixed dose of 30,000 units on days 1, 8 and 15 is used irrespective of the patient's size. Also, many of the new SACT agents, particularly the TKI and MTOR drugs (see Chapter 2) are generally used at a standard flat dose irrespective of the patient's size and age.

Dose reduction

It is important to avoid unnecessary routine dose reductions solely on the basis of transient toxicity, particularly in curative and adjuvant treatments. Most modern protocols and clinical trial publications give clear advice on how best to reduce doses either across the regimen or for individual drugs in response to excess toxicity and using these can help maintain optimal care.

Elderly patients

Appropriately used chemotherapy can bring similar benefits in the elderly as in younger patients. However, the elderly metabolise drugs more slowly and are less resistant to side effects or complications. Whilst it is

important that elderly patients have access to SACT treatments, it is also prudent to consider organ dysfunction carefully when starting treatment, often with dose adjustments from standard doses when starting. The emerging subject of geriatric oncology is exploring this area and many revised protocols for the elderly are being published.

Pretreatment procedures and investigations

Informed consent

Printed information on individual drugs or regimens is usually available and should be used to supplement oral information. The NHS patient 'information prescription' system has large amounts of local and national information readily available. All patients should be given a clear explanation of the purpose of treatment, its possible benefits and risks, clear advice about watching out for possible neutropenic fever and other serious toxicities and what to do if they occur. The advice must include essential 24-hour contact telephone numbers at the hospital, which must also be sent to the patient's GP.

Cardiotoxic drugs

Patients treated with cardiotoxic drugs such as anthracyclines and trastuzumab should have a pretreatment cardiac assessment, such as a multi-gated acquisition (MUGA) scan. This is especially important if the patient is elderly or has a history of cardiac disease, previous anthracycline exposure or mediastinal radiotherapy. Repeat monitoring should be performed according to the specific regimen protocol. Care should be taken to avoid exceeding the recommended total lifetime doses of anthracyclines, particularly when different courses of chemotherapy are given over long periods of time or at different hospitals.

Renal function

A number of drugs including methotrexate and carboplatin are excreted by the kidney and an assessment of renal function by ^{51}Cr-EDTA clearance should be done before starting treatment. The renal function may change during treatment, particularly when using a nephrotoxic drug such as cisplatin, and repeat measurements of renal function by ^{51}Cr-EDTA or calculated values are important to avoid toxicity. If there is significant decline in GFR below 50–60 mL/min, carboplatin at an AUC of 4–5 replaces cisplatin in many regimens. Information on the appropriate dose reduction in renal impairment will be found in most protocols or national guidelines.

Hepatic function

The majority of SACT drugs are wholly or partly metabolised in the liver. The capacity of the liver to handle the drugs is large and the need for dose reduction is relatively uncommon. However, some drugs, including doxorubicin, do need dose reductions in the presence of hepatic impairment, and liver function tests, bilirubin, transaminases and alkaline phosphatase should be reviewed before treatment. Increase in the alkaline phosphatase, alone or accompanied by slight increases in transaminases, does not usually require dose reduction. However, the dose of drugs metabolised in the liver should be reduced if bilirubin is raised, particularly if accompanied by increases in transaminases. The dose of irinotecan, which is excreted in the bile, has to be reduced if the serum bilirubin level is raised. The treatment protocols in most units include advice on appropriate dose reductions. Other sources of advice include the websites of the British Columbia Cancer Agency and the London Cancer Alliance (http://www.bccancer.bc.ca/ and http://www.londoncanceralliance.nhs.uk/, accessed January 2015).

Baseline assessments of tumour

A baseline and regular objective measurements of response are required to assess whether the patient is benefiting from SACT treatment, except for those having adjuvant treatment. This may be by direct physical measurement of visible or palpable tumour, radiological examination, biochemical tests or measurement of tumour markers. When the main aim is symptom control, the patient's symptoms should be monitored carefully and balanced against the treatment toxicity.

Central venous access

Patients who have chemotherapy through ambulatory infusion devices must have central venous access, using a Hickman® or PICC line. Patients with poor veins or those who are to receive multi-day infusions may also need central lines early in their treatment. Although many patients do not have any problems with these

lines, up to 11% develop line-related thromboses and 19% line infections. Patients should therefore be monitored regularly for these problems (Minassian *et al.*, 2000) and the use of subcutaneous ports in place of external catheters should be considered (Estes *et al.*, 2003).

Height and weight

To calculate BSA, height and weight measurements are needed. The patient's body weight should be measured before each new course of chemotherapy, and again if there is reason to suspect that it has altered by more than 5%. If the dose is calculated on the body weight alone, small changes in weight will have a greater impact on the dose and the patient's weight should be checked regularly; for example, every three months, or if the body weight is thought to have changed by more than 5%.

Checks before each SACT cycle

Full blood count

The patient's full blood count should be taken on the day of treatment or the day before. A finding of significant neutropenia or thrombocytopenia will mean a treatment delay. Patients who are anaemic rarely require a delay in chemotherapy (see below). Patients who are admitted with neutropenic fever or who have had more than one delay in treatment during a course of chemotherapy will require a dose reduction if receiving palliative treatment or support with growth factors if they are receiving curative or adjuvant treatment.

Biochemical, renal, liver and bone profile

A full biochemical profile is required before treatment to ensure that there has been no significant change in renal or hepatic function. If there is deteriorating renal or hepatic function, some drugs may need dose reduction or to be changed to an alternative, according to the local protocols. Some patients who experience disease-related hepatic or renal impairment may no longer need a dose reduction if these improve with treatment.

Some drugs have individual specific toxic effects that require additional monitoring. For example, cisplatin treatment frequently increases the renal excretion of potassium and magnesium and in addition to supplements in the i.v. hydration regimen additional oral supplements may be needed. Some of the newer SACT agents have novel side effects including hypothyroidism that may need specific monitoring.

Tumour markers

In malignancies with circulating tumour markers, measuring them can be a rapid, simple way of monitoring the response to treatment. Tumour markers are most useful in gestational choriocarcinoma, in which human chorionic gonadotrophin (hCG) is produced by all tumours (Sita-Lumsden *et al.*, 2012). In advanced testicular cancers, approximately 60% of tumours make one or both of hCG and alpha feto-protein (AFP). These can be used to monitor response or to prompt a change to second-line therapy when the rate of fall is inappropriately slow (Toner *et al.*, 1990). Other tumour markers which can be used for monitoring include CA125 in ovarian cancer, CA15-3 in breast cancer, CA19-9 in pancreatic cancer, carcino-embryonic antigen (CEA) in lower GI malignancies and prostate-specific antigen (PSA) in metastatic prostate cancer.

Major toxicities and their management

This section looks at practical issues in managing SACT toxicities. The main toxicities of individual cytotoxic chemotherapy drugs are summarised in the Appendix (see p. 7).

Myelosuppression

Primary and secondary prophylaxis

If a patient receiving palliative chemotherapy is admitted with neutropenic fever or has persistently low neutrophil counts without fever the dose of the next course should be reduced. However, patients receiving curative (including adjuvant) treatment should receive granulocyte colony stimulating factor (G-CSF) as secondary prophylaxis. For patients on very myelosuppressive regimens the ASH/ASCO guidelines recommend the use of G-CSF from cycle 1 for regimens with a greater than 20% risk of neutropenic sepsis in the first cycle (Smith *et al.*, 2006), as primary prophylaxis, although this is not widely accepted UK practice.

There are some practical problems with the timing and administration of growth factors which can be

Appendix Cancer treatment drugs and their major toxicities

Drug/class	Myelosuppression (0/+/++/+++)	Emetogenic risk (0–5)	Other major toxicities	Notes
Alkylating agents				
Bendamustine	++	3	Hypersensitivity	
Cyclophosphamide	++	4–5	Haemorrhagic cystitis	May need mesna
Dacarbazine	+++	5	Hepatotoxic	Vesicant
Ifosfamide	++	3	Haemorrhagic cystitis Encephalopathy	Needs mesna routinely to prevent haemorrhagic cystitis
Lomustine	+++ Delayed myelosuppression	3	Pulmonary Renal	Capsules 40 mg
Anthracyclines				
Doxorubicin	+++	4	Cardiotoxic Alopecia	Vesicant, give by bolus injection or centrally
Epirubicin	+++	4	As above	As above
Liposomal doxorubicin	+++	2	PPE Cardiotoxic	Exfoliant
Mitomycin	+++ Delayed myelosuppression	2	Renal	Vesicant
Mitozantrone	+++	2	Cardiotoxic	Exfoliant
Anti-metabolites				
Capecitabine	+	2	PPE	Tablets 500 mg, 300 mg and 150 mg
Fludarabine	+++	1	Diarrhoea	Consider PCP prophylaxis
Fluorouracil	+	2	Diarrhoea	PPE with long infusion
Gemcitabine	+	2	Influenza-like reactions after infusion	
Methotrexate	+	3	Mucositis and renal toxicity in high dose	Note drug interactions. Avoid in patients with pleural effusions or ascites
Pemetrexed	+++	2	Mucositis and hepatic toxicity	Toxicity reduced with folate and B12 supplement
Vinca alkaloids and etoposide				
Vincristine	Minimal	1	Neurotoxic	Must be given by intravenous injection only. Vesicant. Max. dose 2 mg
Vinblastine	+	1	Neurotoxic	Must be given by intravenous injection only. Vesicant. Max. dose usually 10 mg

Appendix *(cont.)*

Drug/class	Myelosuppression (0/+/++/+++)	Emetogenic risk (0–5)	Other major toxicities	Notes
Vinorelbine	+	1	Neurotoxic	Oral form (capsules) or intravenous injection only. Vesicant. Max. i.v. dose 60 mg
Vinflunine	+++	3	Constipation	
Etoposide	++	2	Alopecia.	Oral form (large capsules) twice i.v. dose
Platinums				
Cisplatin	+	5	Nephrotoxic Neurotoxic	Exfoliant. Check renal function carefully; good pre- and post-hydration essential
Carboplatin	++ Especially platelets	4	Less nephrotoxic than cisplatin	Hypersensitivity reactions common
Oxaliplatin	++	3	Neurotoxic	Exfoliant. Hypersensitivity reactions
Taxanes				
Cabazitaxel	++	1	Hypersensitivity Diarrhoea	Premedicate prior to infusion
Paclitaxel	++	2	Alopecia Neurotoxic	Vesicant. Hypersensitivity reactions – needs premedication
Docetaxel	+++	2	Alopecia	Vesicant. Hypersensitivity reactions – needs premedication
Topoisomerase 1 inhibitors				
Irinotecan	++	3	Diarrhoea Cholinergic syndrome	May need atropine
Topotecan	+++	2	Alopecia	Exfoliant
Other cytotoxics				
Bleomycin	No	1	Pulmonary Skin	
Eribulin	++	1	Alopecia, fatigue, neuropathy	
Procarbazine	+	5		Weak MAOI; avoid alcohol
Trabectedin	+++	2	Hepatic toxicity	Pretreatment dexamethasone must be given

MAOI, monoamine oxidase inhibitor; PCP, pneumocystis pneumonia; PPE, palmar–plantar erythrodysaesthesia.

overcome with the use of pegylated G-CSF (Neulasta®), needing only a single administration, generally 24 hours after chemotherapy. Studies have shown Neulasta® to be more successful in preventing neutropenic sepsis and better tolerated than daily G-CSF. Although Neulasta® is currently more expensive than daily G-CSF, it may be more cost-effective overall.

Prophylactic antibiotics

The results of the significant trial showed that patients given a prophylactic quinolone antibiotic had fewer admissions for neutropenic fever (Cullen *et al.*, 2005) and so these are now often incorporated into some chemotherapy protocols. Regimens that cause prolonged myelosuppression, particularly lymphoma regimens with long-term steroid administration, also often include co-trimoxazole to reduce the risk of *Pneumocystis carinii* infection.

Anaemia

Many cytotoxic drugs, particularly cisplatin, cause a gradual reduction in haemoglobin levels over the course of treatment. This usually does not lead to dose reductions or delays in treatment, but can significantly affect the patient's quality of life, and an elective blood transfusion may be appropriate. In some patients, erythropoietin may be a reasonable option, but has side effects such as nausea, pyrexia, headache, arthralgia and an increased risk of thrombosis.

Nausea and vomiting

The problems of chemotherapy-associated nausea and vomiting are much less since the introduction of the 5-HT3 antagonist drugs such as ondansetron and granisetron. It is now very unusual for patients to require hospital admission for control of vomiting. So, although many new cancer patients will expect nausea and vomiting to be a major problem, they can be reassured that, with appropriate use of anti-emetics, this is now very unlikely.

Anticipatory nausea and vomiting

Anticipatory nausea and vomiting occur before and during administration of chemotherapy, and are mainly due to the psychological effects associated with previous treatment and poor control of emesis. The problem can be managed by offering lorazepam 0.5–1 mg sublingually or orally immediately before chemotherapy and/or on the previous evening.

Acute nausea and vomiting

Acute nausea and vomiting are defined as occurring up to 24 hours after chemotherapy administration. The drugs used in prevention depend on the emetogenic potential of the regimen, and they are used in a stepwise fashion (Herrstedt *et al.*, 2005). All chemotherapy units will have guidance on which anti-emetics to use with each chemotherapy drug or regimen. Oral metoclopramide or domperidone are usually recommended for drugs of low emetogenic potential, such as bleomycin, vindesine or gemcitabine. However, the majority of drugs and regimens require more powerful anti-emetics, generally a 5-HT3 antagonist such as ondansetron and granisetron, and dexamethasone, on the day of treatment and for one to two days afterwards.

Some new anti-emetic drugs have been developed and licensed recently, including aprepitant, a neurokinin-1 receptor antagonist, useful in patients with poorly controlled emesis, and palonosetron, a long-acting 5-HT3 antagonist and the dissolving film form of ondansetron, which is easier for patients to take.

Delayed nausea and vomiting

The incidence of delayed nausea and vomiting is higher when there is poor control during the acute phase. The 5-HT3 antagonists are generally ineffective in controlling delayed nausea and vomiting, and metoclopramide is usually added to anti-emetic regimens. Cyclizine may be used during prolonged oral regimens if metoclopramide is ineffective in controlling delayed nausea and vomiting.

Cardiotoxicity

Cumulative cardiac toxicity is a problem associated with anthracyclines, and treatment should remain within the standard guidelines for the total lifetime dose – 450 mg/m^2 for doxorubicin. Cardiac function should be monitored more closely in patients with pre-existing cardiac problems and in patients who have received previous treatment with anthracyclines or mediastinal radiotherapy. A number of other drugs can also occasionally cause cardiotoxicity: fluorouracil may cause cardiac ischaemia and arrhythmias and cisplatin can occasionally cause vasospasm and angina or, rarely, stroke.

Renal toxicity

Although renal function is monitored before each chemotherapy cycle in most regimens, particular

attention is needed for drugs that are either renally toxic in themselves or are excreted by the kidneys. Renal toxicity is most often caused by cisplatin. Appropriate treatment modifications should be made if there is a significant rise in the serum creatinine while on therapy, pending a more accurate assessment of renal function such as a ^{51}Cr-EDTA clearance. High-dose methotrexate can also cause renal toxicity and both cyclophosphamide and ifosfamide can cause both renal toxicity and haemorrhagic cystitis.

Diarrhoea

Diarrhoea can be a dose-limiting toxicity with capecitabine and fluorouracil and may also occur as part of the cholinergic syndrome caused by irinotecan. It is important to recognise the symptoms early and to start treatment with fluids, rehydration salts and loperamide.

Palmar–plantar erythrodysaesthesia (hand-foot syndrome)

Palmar–plantar erythrodysaesthesia (PPE) consists of swelling, redness, pain and, occasionally, blistering on the palms of the hands and/or the soles of the feet. It is a common dose-limiting toxicity with capecitabine and liposomal doxorubicin. Patients should be encouraged to use emollients, but effective prevention is difficult. A dose delay is usually required for grade 2 or greater PPE.

Alopecia

Alopecia can be a very distressing side effect of chemotherapy treatment for some patients. The problem can be minimised to some extent by the use of scalp hypothermia in patients receiving bolus injections or short infusions of doxorubicin, epirubicin and docetaxel. However, many patients do develop significant alopecia and they need to be aware of this possibility. Arrangements should be offered for the provision of wigs and alternatives such as head scarves.

Post-chemotherapy fertility

Chemotherapy can affect the patient's fertility. The regimens used in the treatment of testicular cancer, Hodgkin lymphoma, and high-grade NHL tend to have a relatively modest impact on fertility, but it is good practice to offer sperm storage for men undergoing chemotherapy. The situation for women is less satisfactory because techniques for the preservation of oocytes or ovarian tissue are not yet reliable or widely used. Embryo storage is time-consuming and may cause an inappropriate delay in starting treatment.

Surprisingly, the incidence of foetal abnormalities born to patients who have previously completed chemotherapy appears to be similar to that in the normal population. Patients should be advised to defer pregnancy for 12 months after the completion of treatment, but there is little evidence to say whether or not this is too cautious. In addition to the potential risk of foetal abnormalities, the risk of relapse needs to be taken into account when giving patients advice about the timing of future pregnancies. More detailed information on cancer treatment, chemotherapy and fertility is readily available (Lee *et al.*, 2006).

Phlebitis and extravasation

Phlebitis is a common problem with irritant drugs such as dacarbazine, the alkylating agents and vinca alkaloids. These drugs should always be given as bolus injections through a fast-flowing drip or central line. Some drugs, especially anthracyclines, are vesicant and, in the event of extravasation, can cause local tissue necrosis. The patient may report pain on injection, but there may not be any obvious local reaction. There are a number of general and individual drug-specific measures for the treatment of suspected extravasation and the problem should be dealt with as an emergency (see Chapter 8). If extravasation occurs, the drug infusion should be stopped immediately and the local policy on management followed, including referral to plastic surgery if needed. Fortunately, significant extravasations are rare in modern chemotherapy units, but an advance awareness of the local extravasation policy may help urgent care to be delivered more effectively in the event of an occurrence.

Safe administration of chemotherapy

In the UK, there are national standards for the safe prescribing, dispensing and administering of chemotherapy. The standards, and methods of auditing these, vary in detail, but every organisation that provides chemotherapy has the responsibility to maintain policies and procedures to ensure that these standards are met. Training, competency and adequate facilities are the keys to safely prescribing, dispensing and administering chemotherapy. All healthcare staff involved in chemotherapy must be aware of their local policies.