1 PRACTICAL ISSUES IN CYTOTOXIC CHEMOTHERAPY USAGE

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Introduction

In this chapter, the principles of cytotoxic chemotherapy treatment and the appropriate use of anticancer drugs, including some of the new targeted drugs, will be discussed. It will not be possible to give a comprehensive description of every drug and regimen, and standard chemotherapy textbooks (e.g. Allwood *et al.*, 2002; Summerhays and Daniels, 2003) or specialist websites (e.g. BC Cancer Agency, www.bccancer.bc.ca/default.htm) should be consulted for this information. However, this chapter should provide chemotherapy prescribers and administrators with enough information to discuss treatments with patients, to prescribe chemotherapy safely and to manage the common treatment-related side effects.

Aims of chemotherapy treatment

There are three main indications for the use of chemotherapy:

- The management of patients with curable advanced malignancies including choriocarcinoma, testicular cancer, Hodgkin lymphoma and high-grade non-Hodgkin lymphoma (NHL).
- The preoperative or postoperative adjuvant treatment of localised malignancies, primarily breast cancer and colorectal cancer.
- The treatment of patients with advanced incurable malignancies, where the primary aim is palliation and symptom control, sometimes without a major expectation of prolonging survival.

Before starting a course of chemotherapy, both the prescriber and the patient should be clear about the aims of treatment. When chemotherapy is used curatively, it is essential to maintain the calculated dose and dosage schedule according to the treatment protocol. The importance of this has previously been shown for testicular cancer (Toner *et al.*, 2001), for lymphoma (Lepage *et al.*, 1993) and in the adjuvant treatment of breast cancer, where the rate of relapse is higher when the dose intensity is reduced (Wood *et al.*, 1994). Generally, the regimens used in these treatments have significant side effects including neutropenia, and the use of granulocyte-colony stimulating factor (G-CSF) may be required to keep treatment on schedule. However, because there is the clear intent of achieving either cure or, for adjuvant treatment, an increased chance of cure, these side effects and treatment-related risks are seen as acceptable temporary problems.

In contrast, patients having palliative chemotherapy should benefit by experiencing an improved quality of life. An increase in overall survival is not usually the primary aim of treatment and very toxic treatments are not usually justified. In this case, maintaining dose intensity is not so important and dose reductions can be made to ensure that the patient safely tolerates the treatment.

Cytotoxic chemotherapy: mode of action

Cytotoxic chemotherapy drugs are systemic therapies that aim to kill or slow the growth of tumour cells while being relatively sparing to normal cells. The sensitivity of different tumour types to the actions of chemotherapy drugs varies widely among the cells of origin and across the range of drugs. In curable cancers, malignant cells can be many times more sensitive to cytotoxic drugs than the cells they have arisen from and, fortunately, more sensitive than the cells of the bone marrow. In the more common malignancies, tumour cells are generally more sensitive to cytotoxic drugs than are their parent cells, but they are insufficiently sensitive to achieve a cure.

Alongside this major divide between the differing types of malignancy, there is a wide range of activity of the different chemotherapy drugs across the different tumours.

Whereas the majority of chemotherapy drugs have been developed empirically, the mechanisms for the greater effectiveness of some drugs in some tumours

are now becoming better understood. For example, capecitabine is metabolised to the active drug fluorouracil by thymidine phosphorylase, which is present in greater concentrations in some types of tumour cells than in normal cells.

Cell-cycle specificity

Historically, the mode of action of many chemotherapy drugs has been divided between those termed 'cell-cycle specific' and those that are 'cell-cycle non-specific.' The cycle-specific drugs, such as the antimetabolites (methotrexate, fluorouracil and gemcitabine), interact predominantly with cells that are actively synthesising new DNA in the S phase. These drugs are most effective in tumours with high mitotic indices and they produce greater cell kill if given in prolonged exposures, killing larger numbers as cells move through to the S phase.

In contrast, the cell-cycle non-specific drugs interact with cells in all parts of the cycle and they can be cytotoxic to more slowly proliferating tumour cells. The common cell-cycle non-specific drugs such as the alkylating agents and the antitumour antibiotics have activity at all phases of the cell cycle, and cell killing is more closely linked to the total dose rather than to the duration of administration.

Although the cell-cycle distinction has been of great value in developing drug protocols and combinations, modern research suggests that this distinction is relatively crude and in fact most drugs have actions against both dividing and resting cells. However, the distinction is of some use in anticipating the side effects of chemotherapy, where the extended use of cell-cycle-specific drugs can lead to major problems with neutropenia and mucosal damage.

Chemotherapy scheduling and regimens

Combination chemotherapy regimens

When cytotoxic drugs are developed and licensed, it is usually on the basis of data that have been obtained in trials using single agents. After this initial approval, new drugs are generally combined with others into combination chemotherapy schedules. Single-agent therapy does remain a part of palliative chemotherapy for several tumour types; however, the best results from chemotherapy are usually with a combination of drugs, each of which is active in the tumour type as a single agent. In general, the principles of choosing combinations of chemotherapy are as follow:

- Each drug is active 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.

The bleomycin, etoposide, cisplatin regimen used for the treatment of advanced testicular cancer gives one of the best examples of the benefits derived from combining chemotherapy agents. In this regimen, bleomycin, etoposide and cisplatin have all been shown to have significant activity as single agents, but their durations of response are generally short. The three drugs have different patterns of dose-limiting toxicities. Bleomycin carries a risk of pulmonary toxicity, but it causes minimal myelosuppression; the dose of cisplatin is limited by renal toxicity, but it also causes minimal myelosuppression; and etoposide is highly myelosuppressive, but it has no significant pulmonary or renal toxicity. By combining these drugs with their differing patterns of toxicity, each can be used at nearly the full single-agent dose. The impact of this approach to chemotherapy treatment has been central in producing an overall cure rate of greater than 80% for patients with advanced testicular cancer (Williams *et al.*, 1987).

The treatment of high-grade B-cell NHL provides a similar example of effective combination chemotherapy and the benefits of adding in a modern drug with a completely different mode of action. Since its introduction in the 1970s, cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy has been the standard of care for high-grade B-cell NHL. In this regimen, two myelosuppressive drugs, cyclophosphamide and doxorubicin, are combined with vincristine and prednisolone, which are non-myelosuppressive. Over the past 20 years, there have been several important trials that have tested more toxic and complex regimens against CHOP, with negative results (Fisher *et al.*, 1993; Gordon *et al.*, 1992). However, the more recent addition of an anti-CD20 monoclonal antibody, rituximab, to CHOP has brought an increase in the event-free survival at 5 years from 29% to 47% (Feugier *et al.*, 2005). Rituximab has a completely different mode of action from that of conventional cytotoxic drugs and it rarely causes significant side effects. The combination of rituximab with CHOP chemotherapy is now standard

practice, and it represents the first major change to high-grade NHL management in 15 years.

Another monoclonal antibody, trastuzumab, is bringing about exciting results in the treatment of breast cancer. Early results suggest that the addition of trastuzumab to conventional adjuvant chemotherapy results in an approximately 50% decrease in the risk of relapse measured at two years, and there is a realistic expectation that this will translate to higher overall survival figures as the trial data mature (Piccart-Gebhart *et al.*, 2005; Romond *et al.*, 2005).

Protocols and guidelines

The introduction of peer-reviewed treatment policies within the National Health Service (NHS) has led each cancer network and NHS Trust that treats cancer to have formal protocols of their approved chemotherapy regimens. These regimens should be familiar to the health professionals who dispense and administer them, and 'off-protocol' regimens should not generally be prescribed unless there is good evidence in the research literature to do so.

Scheduling and administration of chemotherapy

Generally, the scheduling and administration of chemotherapy follow the protocols used in the original clinical trials. Although the precise sequence of giving drugs in many regimens is relatively unimportant, there are some situations where drugs must be given in the correct order.

The most frequent situation where this applies is the combination of paclitaxel and carboplatin in the treatment of patients with ovarian cancer. Carboplatin is a cell-cycle non-specific drug; thus, it would be suited to bolus administration in a single large dose. However, because of the risk of hypersensitivity, it is given as an infusion over a minimum of 30 minutes rather than as a bolus. It is also potentially unstable, especially in poly(vinyl choride) (PVC) containers, and so the final volume of the infusion is also critical. The myelosuppression nadir from carboplatin is between 14 and 21 days, which would indicate administration using a 28-day cycle.

Paclitaxel is cell-cycle specific and so ideally it should be given in multiple fractions over a prolonged period. The original phase III trials, which were completed before licensing, administered the drug over 24 hours. However, this presents logistical problems; thus, more recent studies such as the International Collaborative Ovarian Neoplasm (ICON) 3 trial have used a 3-hour infusion (ICON Group, 2002). Attempts to reduce this to 1 hour have resulted in a number of hypersensitivity reactions, and most centres continue with a 3-hour infusion. The nadir of myelosuppression from paclitaxel occurs after 10 days, indicating a maximum cycle length of 21 days. Combining the two drugs presents a dilemma about the length of the cycle, but trials have shown that a 21-day cycle does not produce unacceptable myelosuppression and it removes the theoretical possibility of tumour growth attributed to suboptimal scheduling of paclitaxel.

Paclitaxel also causes hypersensitivity reactions, mainly because of the need for a solubiliser to allow the drug to dissolve. It too has stability problems and it needs administration through non-PVC lines.

Finally, in routine practice, paclitaxel is administered before carboplatin, with a premedication of a corticosteroid, antihistamine and H2 antagonist. When used in this sequence, the safety profile is consistent with that reported for single-agent use. In contrast, in studies when paclitaxel was given after carboplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance.

Calculation of doses

Body surface area

The ideal method of calculating a suitable dose of a cytotoxic drug would take into account its pharmacokinetic properties – the ability of the body to deliver the drug to its site of action and the subsequent metabolism and excretion. The dose of the drug could then be adjusted further depending on the actual toxicity seen in each patient. However, although more precise and individualised approaches to chemotherapy drug dosing are often 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 interestingly 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 so the method used may vary among centres but there is generally good correlation among the methods.

Dose capping

Using the calculated BSA in large and obese patients may lead to relative overdosing of chemotherapy with an associated risk of excess toxicity. To place an upper limit on drug dose, dose capping is frequently used, and many institutions will use 2.2 m^2 as an upper limit for curative and adjuvant treatments and 2 m^2 for palliative treatments. However, care should be taken when prescribing for tall, non-obese individuals because there is a potential risk of underdosing if the BSA is capped at 2.2 m^2.

An exception to the 2.2 m^2 cap is with the use of vincristine; with this drug, the dose is usually capped at 2 mg, so although the dose is 1.4 mg/m^2 in the CHOP regimen, all but the smallest patients receive a capped dose of 2 mg.

Area under the curve (AUC) dosage

Among the commonly used chemotherapy drugs, carboplatin is the only one to have its dose calculated directly according to the renal function. This drug is excreted unchanged by the kidneys, and a formula has been developed (the Calvert equation) which is based on renal function (Calvert *et al.*, 1989). The desired AUC (area under the curve of serum levels against time) is chosen, and the dose is calculated by the following formula:

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

The GFR is the glomerular filtration rate. The Calvert equation was developed using the more accurate EDTA clearance as the measure of GFR. If the GFR is calculated from serum creatinine using the Cockcroft-Gault formula (see following text), a correction, such as multiplying by 1.1, should be applied.

Body weight dosing

Body weight alone is not used often in calculating doses of cytotoxic drugs. However, some of the newer drugs, such as the monoclonal antibody trastuzumab, are calculated on body weight alone.

Flat dosing

Bleomycin is the only commonly used cytotoxic drug for which a fixed dose is employed. In the treatment of testicular cancer, a fixed dose of 30 000 units is used irrespective of the patient's BSA.

Pretreatment investigations and checks

Before initiating chemotherapy

Informed consent

Information on individual drugs or regimens is usually available in a written form and should be used to supplement verbal information. In addition to an explanation of the purpose of treatment and the adverse effects of the drugs, patients should be given clear advice about monitoring for, and action on, suspected neutropenic fever and other serious adverse effects of chemotherapy. This must include 24-hour contact telephone numbers at the hospital.

Cardiotoxic drugs

For patients on cardiotoxic drugs such as doxorubicin or the other anthracyclines, pretreatment cardiac assessment, such as a MUGA scan, is recommended, especially if the patient has a history of cardiac disease, is elderly, or has had previous anthracycline exposure or mediastinal radiotherapy. Repeated monitoring of cardiac function should be performed according to the protocol being followed, and care should be taken to avoid exceeding the lifetime dose recommendations if more treatment is given at a later date.

Renal function

An accurate measurement of renal function, such as an EDTA clearance, is generally required for carboplatin, for which the dose is calculated according to the GFR. Accurate assessment is also recommended for treatments using cisplatin, because this drug is significantly nephrotoxic. If there is evidence of a significant decline in renal function, the cisplatin in the regimen can generally be amended by substituting carboplatin, usually at an AUC of 4 or 5. For other drugs and for continuing assessment of renal function, the creatinine clearance (CrCl) can be calculated from the serum creatinine using the Cockcroft–Gault formula as follows:

$$\text{CrCl} = \frac{\text{F} \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{Serum creatinine}(\mu\text{M/l})}$$

$$\text{F} = 1.04 \text{ (females) or } 1.23 \text{ (males)}$$

Doses will need to be amended for drugs that are excreted renally if there is a reduced GFR. Information on the appropriate dose reduction in renal impairment will be found in most protocols or national guidelines, such as those available online from the North London Cancer Network (www.nlcn.nhs.uk/professional.php).

Hepatic function

Most drugs undergo some metabolism by the liver. The capacity of the liver to handle drugs, even when there is hepatic impairment, is large, and the need for dose reductions is relatively uncommon. However, some drugs, including doxorubicin, do need dose reductions in the presence of hepatic impairment, and the liver function tests, bilirubin, transaminases and alkaline phosphatase should be reviewed before treatment. Increases in the alkaline phosphatase, alone or accompanied by slight increases in transaminases, do not usually require dose reductions, but elevation of bilirubin, particularly if accompanied by increases in transaminases, usually requires the dose reduction of drugs that are metabolised in the liver. Irinotecan, which is excreted in the bile, has to be dose-reduced in the presence of elevated serum bilirubin. The treatment protocols in most units include advice on appropriate dose reductions; other sources of advice include the websites of the BC Cancer Agency and the North London Cancer Network.

Baseline assessments of tumour

With the exception of adjuvant treatment, a baseline measurement and regular objective measurement of response are required to assess whether the patient is benefiting from chemotherapy. This can involve direct physical measurement of the tumour, radiological examination, biochemical tests or measurement of tumour markers, depending on the disease site. Where the principal aim is palliative, one should also monitor symptomatic benefit carefully and balance this against the treatment toxicity.

Central lines

Patients who have chemotherapy through ambulatory infusion devices must have central access before treatment, using a Hickman® or PICC line. Patients with poor veins or those who are to receive multiday infusions will also benefit from central lines early on in their treatment, if possible. Although many patients do not experience any problems with these lines, studies have shown that up to 11% develop line-related thromboses, and 19%, line infections. Patients should therefore be monitored regularly for these problems (Minassian *et al.*, 2000).

Height and weight

To calculate BSA, height and weight measurements are needed. The patient's body weight should be measured before each course of chemotherapy, and again if there is reason to suspect that it has altered by more than 5%. Where the dose is calculated on the body weight alone, smaller changes in weight have a greater impact on the dose and, in this situation, 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%.

Before each cycle

Full blood count

The patient's full blood count should be taken close to the actual day of administration, ideally on the day of treatment or the day before. Significant neutropenia or thrombocytopenia will mean a treatment delay. Patients who are anaemic rarely require a delay in chemotherapy and can be transfused if their haemoglobin level drops below 9.5 g/dl or if they develop symptoms of anaemia.

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 due to either the treatment or the tumour. In response to deteriorating renal or hepatic function, some drugs may need dose reduction or a change to alternative therapies. Some patients who presented with disease-related hepatic or renal impairment may no longer need a dose reduction if these parameters return to normal with effective treatment.

Some drugs have specific toxic effects that require monitoring. For example, cisplatin increases the renal excretion of potassium and magnesium and oral supplementation is required frequently. The typical practice in the United Kingdom (UK) is to add 20–40 mM of potassium and about 8 mM of magnesium per day to hydration fluids.

Tumour markers and other tests for response

If a tumour secretes circulating tumour markers, measuring these can be a rapid, simple and economic method to monitor the response of the tumour to treatment. Tumour markers are most useful in gestational

choriocarcinoma, where human chorionic gonadotrophin (HCG) is constitutively produced by all tumours, and they provide an excellent method of following response to treatment. In advanced testicular cancers, approximately 60% of tumours make one or both of HCG and alpha feto-protein. These can be used to monitor response or to indicate a change to second-line therapy when the rate of fall is inappropriately slow (Toner *et al.*, 1990).

Other tumour markers are also used in the assessment of some other malignancies, such as cancer antigen 125 in ovarian cancer and prostate-specific antigen in metastatic prostate cancer.

Major toxicities and their management

This section looks at practical issues of managing chemotherapy toxicities. The main toxicities of individual chemotherapy drugs are summarised in the Appendix (see p. 11).

Myelosuppression

Neutropenic fever and neutropenic sepsis

The most frequent serious complications of chemotherapy treatment are neutropenic fever and neutropenic sepsis. Although the nadir of neutropenia varies among drugs (e.g. patients on docetaxel can become neutropenic two to three days after treatment, and the nadir for mitomycin C is several weeks after treatment), the risk of neutropenia should be considered at all times during the course of chemotherapy treatment.

Patients with neutropenic fever or neutropenic sepsis must be treated promptly using the local policies for the empirical treatment. The treatment plan with intravenous antibiotics will usually include an aminoglycoside and an antipseudomonal antibiotic or a cephalosporin and vancomycin. Patients with an apparent site of infection, such as chest infection, urinary tract infection or central-line sepsis, should also receive an antibiotic with appropriate additional cover.

Most patients with neutropenic fever will initially appear well, apart from the pyrexia, and they will respond to treatment with intravenous or oral antibiotics. However, a number of patients can either present or rapidly become seriously unwell with hypotension, shock and end-organ failure. In these patients, rapid assessment and management are essential. Volume replacement with intravenous fluids must be initiated, and consideration should be given to transfer to a high-dependency or intensive-care unit. All patients with neutropenic sepsis can deteriorate very quickly, and junior medical staff must be made aware of the need to contact more senior staff, if necessary, for advice on the management of such patients. Neutropenic fever and sepsis are also considered in Chapter 6 (see p. 77).

Primary and secondary prophylaxis

Patients receiving palliative chemotherapy who are admitted with neutropenic fever, or those who have persistently low neutrophil counts without fever, should generally have dose reductions made to their treatment. In contrast, patients receiving curative (including adjuvant) treatment should receive G-CSF prophylaxis, as secondary prophylaxis, to prevent further episodes of neutropenia and to maintain dose intensity.

More recently, there has been a move towards primary prophylaxis (i.e. from cycle 1) for patients on very myelosuppressive regimens, and the current ASH/ASCO guidelines recommend this approach for regimens with a greater-than-20% risk of neutropenic sepsis in the first cycle (Smith *et al.*, 2006). However, this is not yet standard practice in the UK.

Practical issues with the timing and administration of growth factors can be a problem, but this has been overcome with the introduction of pegylated G-CSF (Neulasta®), which requires only a single administration, generally 24 hours after chemotherapy administration. Studies have demonstrated Neulasta® to have been more successful in preventing neutropenic sepsis than daily G-CSF and to have improved patient tolerability. Although Neulasta® is more expensive than daily G-CSF, it may be cost effective when compared to the costs of a hospital admission for neutropenic fever.

Prophylactic antibiotics

The Significant trial showed a small, but definite, reduction in the incidence of admissions for neutropenic fever for patients with solid tumours who were given a prophylactic quinolone antibiotic (Cullen *et al.*, 2005). The data from this study, and the increasing evidence that prophylactic growth factors are clinically and economically effective, are leading many centres to incorporate their use into routine protocols.

In regimens that cause prolonged myelosuppression, particularly lymphoma regimens with long-term steroid administration, patients will benefit from the use of co-trimoxazole to reduce the risk of pneumocystis carinii infection.

Prophylactic antibiotics are also considered in Chapter 6 (see p. 79).

Anaemia

Some commonly used cytotoxic drugs, including cisplatin, cause a gradual reduction in haemoglobin levels over a course of treatment. This does not usually need a dose reduction or delay in treatment, but it can dramatically affect a patient's quality of life. A blood transfusion is standard practice. Erythropoietin may be indicated, but it is expensive and under review by the National Institute for Health and Clinical Excellence (www.nice.org.uk). Erythropoietin is also considered in Chapter 2 (see p. 20).

Nausea and vomiting

The problems of chemotherapy-associated nausea and vomiting have become far less since the introduction of the 5-HT3 antagonist drugs such as ondansetron and granisetron. Many new patients still expect nausea and vomiting to be a major problem, but they can be reassured that, with appropriate use of antiemetics, this is now rare.

Predisposing factors

The predisposing factors for an increased risk of nausea and vomiting include the previous poor control of nausea/vomiting, a history of motion sickness, being of a younger age, being female and having a chronic, low alcohol intake (Gralla *et al.*, 1999). These factors may require increased prophylaxis above those recommended here.

Anticipatory nausea and vomiting

Anticipatory nausea and vomiting occur up to and during administration of chemotherapy, and are mainly due to the psychological effects associated with previous treatment. The management of this problem involves considering a benzodiazepine before treatment and/or on the previous evening. Lorazepam 0.5 to 1 mg sublingually or orally is the drug of choice, and it is well tolerated.

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 level of antiemetics 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 antiemetics, generally a 5-HT3 antagonist and dexamethasone, on the day of treatment and for one to two days afterwards. For patients who continue to have problems, newer drugs, including aprepitant, a neurokinin-1 receptor antagonist, are recommended in addition to 5-HT3 antagonists and corticosteroids.

Delayed nausea and vomiting

The incidence of delayed nausea and vomiting is increased when there is poor control of the acute phase. The 5-HT3 antagonists are not generally effective in treating delayed nausea and vomiting. Cyclizine may be substituted for metoclopramide for the treatment of delayed nausea and vomiting or during prolonged oral regimens if metoclopramide is ineffective. Good antiemetic prophylaxis, and the use of aprepitant or palonosetron with subsequent cycles, may also prevent delayed nausea and vomiting.

Other dose-limiting toxicities

Cardiotoxicity

Cumulative cardiac toxicity is a problem associated with the anthracyclines, and treatment should remain generally within the standard guidelines on total lifetime dose. In the case of doxorubicin, this is 450 mg/m^2. Cardiac function should be monitored more closely in patients with cardiac problems or in patients who have received previous treatment with anthracyclines or mediastinal radiotherapy. A number of other drugs can also occasionally cause cardiotoxicity; fluorouracil is a good example that is linked with cardiac ischaemia and arrhythmias.

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. Cisplatin is the drug that is most frequently linked to renal toxicity. 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 an EDTA clearance or 24-hour CrCl. High-dose methotrexate can also cause renal toxicity, whereas cyclophosphamide and ifosfamide can cause both renal toxicity and haemorrhagic cystitis.

Diarrhoea

Diarrhoea can be a dose-limiting toxicity with the fluoropyrimidines such as capecitabine and 5-FU. Diarrhoea can also occur as part of the cholinergic syndrome, which is seen with irinotecan. It is important to recognise the symptoms early and to start treatment with fluids, rehydration salts and loperamide.

Palmar–plantar erythrodysaesthesia (PPE)

PPE is the 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. Pyridoxine 50 mg three times a day is often used as treatment, but it is not clear how effective it is. Avoidance of heat can help to prevent PPE.

Other toxicities

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 chemotherapy patients do develop significant alopecia and they need to be aware of this possibility. Arrangements should be offered for wigs and other cosmetic supports such as head scarves.

Fertility and foetal abnormalities (contraception)

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 routine 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 a significant 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 are 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 local reactions

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 via fast-flowing drips or through a central line.

Administration issues

Safe administration of chemotherapy

In the UK, there are formal standards for the safe prescribing, dispensing and administration of chemotherapy. The standards, and methods of auditing these, vary in detail among the home countries, 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.

Intrathecal chemotherapy

There have been a number of fatalities from the inadvertent administration of vinca alkaloids by the intrathecal route. Intrathecal chemotherapy must be prescribed and administered only by trained specialist registrars, staff grades and consultants. All prescribers must be aware of the local arrangements for administering chemotherapy and they should refuse to undertake any procedure for which they have not been trained.

Extravasation

A number of cytotoxic drugs are vesicant and, in the event of extravasation, they 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 6, p. 80).

Hypersensitivity and anaphylaxis

Certain cytotoxic drugs, and most monoclonal antibodies, can produce hypersensitivity reactions that can range from a 'flu-like' syndrome to anaphylactic shock. Platinums and taxanes are the cytotoxic drugs that are most commonly implicated. Premedication with corticosteroids, antihistamines and paracetamol may be recommended, depending on the expected reaction. Full resuscitation facilities must be available for patients receiving first doses of agents that are known to cause hypersensitivity. Generally, this involves administration in a hospital setting at a time when staffing levels and skill mix are appropriate to deal with emergencies. Subsequent doses may be given at other locations depending on the risk of future reactions. The detailed treatment of anaphylaxis will depend on local policy but will include epinephrine (adrenaline), and oxygen must be available (see Chapter 6, p. 79).

Cholinergic syndrome

Cholinergic syndrome is seen with irinotecan, and it is characterised by flushing, sweating and diarrhoea. Treatment is with atropine, and premedication with this is recommended for subsequent cycles. Late-onset diarrhoea (more than 24 hours postinfusion) is also seen, and it is treated with loperamide, rehydration, and possibly antibiotics. Patients must be educated to recognise these symptoms and to take appropriate action.

Oesophageal–pharyngeal syndrome

This is seen with oxaliplatin and, although rare, can be very distressing for the patient, who may confuse this symptom with respiratory or cardiac arrest. Avoidance of cold liquids and food and not exposing the body to sudden cold will usually prevent this syndrome, and patients can be reassured if they are warned in advance that this symptom is transient. Treatment is symptomatic; warm drinks often help in mild cases. Prolonging infusion times has been used successfully to reduce the rates of recurrence of oesophageal–pharyngeal syndrome.

Oral chemotherapy and overcompliance

With oral chemotherapy, overcompliance is often a problem when capecitabine is involved: patients may ignore the onset of dose-limiting adverse effects, such as diarrhoea, and then continue treatment and become dehydrated. Careful patient education is essential and treatment must not be started until the prescriber is sure that the patient fully understands how to take the medication, the use of supportive medication, the circumstances when treatment should be discontinued, and how to obtain help.

Summary

The development of effective chemotherapy treatments has been one of the great successes of modern medicine. As a result, most patients with high-grade NHL, Hodgkin lymphoma or testicular cancer are treated with the expectation of cure. Alongside this, the adjuvant treatment of breast and bowel cancer has increased the overall cure rates of these illnesses by at least 10%.

Although these drugs are highly toxic, their use in the modern multidisciplinary cancer centres, following established protocols and patterns of administration, results in relatively little unpredictable toxicity. Most additional information on the safe and effective use of the current drugs is readily available within each unit or on the expert websites. At present, the introduction of new targeted anticancer drugs such as the monoclonal antibodies and kinase inhibitors will be the main area of change in cancer treatment. It is likely that these drugs will be increasingly combined with existing therapies not only to produce enhanced results but also to produce differing patterns of side effects that will require ongoing education and training.

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