

Anaesthetic implications of chemotherapy



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Key points

Chemotherapy causes damage to healthy cells leading to side-effects affecting the respiratory, cardiovascular, renal, hepatic, nervous, gastrointestinal (GI), and haematopoietic systems.

After completion of chemotherapy treatment, some toxic effects must be considered to be long term (e.g. bleomycin and anthracyclines).

The chemotherapy agent bleomycin can cause severe pulmonary fibrosis potentially aggravated by the administration of high concentration oxygen.

The myocardial depressant effect of anaesthetic agents can exacerbate the cardiotoxic side-effects after chemotherapy.

Careful preoperative assessment is essential to identify toxicity and avoid potential complications.

Chemotherapy, radiotherapy, and surgery are the most common modalities used to treat a patient with cancer. Many established chemotherapy drugs are anti-proliferative agents, targeting rapidly dividing cancer cells but also damaging non-malignant dividing cells, leading to toxicity. Chemotherapy usually causes cell death via a drug-receptor interaction that stimulates a cascade of catastrophic events, usually resulting in apoptosis. Common toxicities include cardiac, pulmonary, renal, hepatic, GI, bone marrow, and neurological damage. Table 1 lists the common anticancer action of the frequently used chemotherapy drugs. Newer anticancer agents target other differences between cancer cells and normal cells in order to exert a differential effect but all still have significant toxicity. This article will focus on the challenges that cancer patients receiving chemotherapy present to the anaesthetist.

Timing of chemotherapy and surgery

Chemotherapy has a role in several different clinical settings in the treatment of cancer, which can be broadly classified as:

- neoadjuvant therapy before definitive surgical resection of the primary tumour, metastases, or both. The aims are variable depending on tumour type, aiming to improve the chance of complete resection and survival, or reducing the need for more complex or disfiguring surgery, for example, lumpectomy rather than mastectomy in breast cancer treatment.
- adjuvant therapy after tumour resection, aiming to reduce the risk of tumour recurrence.
- palliative therapy to improve quality of life and prolong survival without the possibility of cure.

Combination chemotherapy is frequently administered to increase cancer cell kill and reduce drug resistance. Drugs chosen may have different mechanisms of action, leading to synergistic effects. Chemotherapy is administered in 'cycles', usually given every 2–3 weeks, usually over a 3–6 month period (but sometimes significantly longer) with recovery phases between each cycle to allow repair of normal tissues and resolution of toxic effects. The use of multidosing regimes will also increase the likelihood of cancer cell death, as when a single dose is administered not all of the cells will be in the susceptible part of the cell cycle.

Patients may therefore present for both elective and emergency surgery after administration of chemotherapy. Table 2 shows a list of common elective procedures performed in cancer patients. In the emergency situation, surgery may be unrelated to ongoing cancer management and may occur during a course of chemotherapy. As a consequence, all anaesthetists should be aware of the potential complications presented by chemotherapy drugs and have an appropriate management plan for their patients.

As part of preoperative assessment, the anaesthetist should take a focused history of cancer management. A detailed drug history includes the precise chemotherapy regime used and any specific toxic effects suffered by the patient. Clinical features of toxicity which may alert the anaesthetist to more serious systemic complications include shortness of breath, palpitations, chest pains, and fever. A thorough examination may also reveal signs that require further investigation before surgery. Routine investigations performed such as full blood counts, blood biochemistry, and an ECG are important in management of the cancer patient before theatre. Other investigations, for example, a chest X-ray, an arterial blood gas, pulmonary function tests, and an echocardiogram

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Table 1 Mechanism of action of chemotherapy drug groups and example drugs for each group

| Drug group | Mechanism of action | Examples |
|----------------------------------|--|------------------------------------|
| Alkylating agents | Cause DNA cross-links and prevent cell replication | Cyclophosphamide, cisplatin |
| Anti-metabolites | Diverse group, for example, may interfere with nucleotide metabolism and thus DNA synthesis and repair | Methotrexate, 5-fluorouracil |
| Topoisomerase interactive agents | Damage DNA via interaction with topoisomerase enzymes | Irinotecan, doxorubicin, bleomycin |
| Anti-microtubule agents | Interfere with mitotic and non-mitotic cellular processes | Paclitaxel |

Table 2 Common elective operations in cancer patients that may follow chemotherapy administration

| Cancer type | Operations | Commonly used chemotherapy drugs |
|------------------------|--|---|
| Breast | Mastectomy, lumpectomy, axillary dissection | Epirubicin, cyclophosphamide, taxol |
| Oesophageal or gastric | Oesophagectomy, gastrectomy | Epirubicin, cisplatin, 5-fluorouracil |
| Bowel | Metastasectomy (liver or lung) | Oxaliplatin, 5-fluorouracil |
| Ovarian cancer | Interval de-bulking surgery (IDS) | Carboplatin, taxol |
| Germ cell tumours | Retroperitoneal lymph node dissection, orchidectomy | Bleomycin, etoposide, cisplatin |
| Osteosarcoma | Amputation, endoprosthetic replacement, metastasectomy | Methotrexate, cisplatin, doxorubicin, ifosfamide, etoposide |

Table 3 Systems-based chemotherapy toxicities and commonly associated chemotherapy drugs. GM-CSF, granulocyte macrophage colony-stimulating factor; BCG, Bacillus Calmette–Guerin

| Organ system | Associated chemotherapy drugs |
|--------------------|---|
| Pulmonary toxicity | Cytotoxic antibiotics (e.g. bleomycin, mitomycin-C, and doxorubicin), nitrosureas (e.g. lomustine), alkylating agents (e.g. cyclophosphamide, ifosfamide, melphalan, chlorambucil), anti-metabolites (e.g. methotrexate, azathioprine, cytarabine, fludarabine), plant alkaloids (e.g. vincristine, vinblastine, etoposide), biological response modifiers (e.g. GM-CSF, interleukin-2, interferon, BCG), others: taxol |
| Cardiotoxicity | Cytotoxic antibiotics; plant alkaloids; alkylating agents; others: 5-fluorouracil, cisplatin, interferon, interleukin-2, taxol |
| Hepatotoxicity | Nitrosureas; anti-metabolites; cytotoxic antibiotics; others: 5-fluorouracil, vincristine, cisplatin |
| Nephrotoxicity | Nitrosureas; others: bleomycin, cisplatin, cyclophosphamide, ifosfamide, methotrexate, mitomycin C, vincristine |

gram, may be required depending upon the treatment regimen used.

A systems approach to toxicity after chemotherapy

The toxic effects of most of the commonly used chemotherapy drugs are well established (Table 3). Some occur acutely, for example, hypersensitivity reactions, or in the short-term, for example, myelosuppression and renal or hepatic impairment, whereas some need to be considered as long-term problems, for example, bleomycin pulmonary toxicity and chemotherapy-related cardiovascular complications.

Respiratory system

Patients receiving chemotherapy who present with respiratory symptoms and signs present a diagnostic challenge: infection, metastatic disease, pulmonary embolism, or drug-induced pulmonary toxicity are possible diagnosis in the cancer patient. Drugs such as bleomycin, cyclophosphamide, nitrosureas, mitomycin, busulphan, and methotrexate commonly cause pulmonary toxicity but many other drugs may also have an association (Table 3).

Initial presentation can be subtle; the patient may be asymptomatic with no loss of physiological function or may complain of a dry cough or increasing breathlessness with exercise. There may be minimal changes on chest X-ray and no marker lesions. The pathogenesis of pulmonary toxicity secondary to chemotherapy is often uncertain. Methotrexate and cyclophosphamide classically cause pneumonitis. Treatment is often unsuccessful and progressive pulmonary fibrosis may ensue.¹

Due to the immunosuppressant effects of chemotherapy drugs (most chemotherapy agents cause myelosuppression including neutropenia), patients may present acutely unwell with infections such as pneumonia. Postoperatively, these patients may require a period of artificial ventilation.

Bleomycin

Bleomycin is a particularly important chemotherapy drug for the anaesthetist to be aware of. Bleomycin is often used to treat germ cell tumours and Hodgkin's disease in a curative setting. The major limitation of bleomycin therapy is the potential for subacute pulmonary damage that can progress to life-threatening pulmonary fibrosis. Pulmonary toxicity occurs in 6–10% patients and can be fatal.² Exposure to high-inspired concentration oxygen therapy,

Table 4 Authors' guidance for oxygen therapy in patients who have received bleomycin¹⁰

| |
|--|
| Summary guidance—oxygen therapy for patients who have received bleomycin |
| Patients have a life-long risk of bleomycin-induced lung injury |
| Oxygen therapy should be avoided if at all possible |
| Clinical procedures (and leisure activities) involving a high $F_{I_{O_2}}$ should be avoided |
| If a patient is hypoxic, O_2 therapy should be minimized to maintain O_2 saturation of 88–92% |
| High oxygen concentrations should be used with extreme caution for immediate life-saving indications only (to maintain O_2 saturation of 88–92%) |

even for short periods, as experienced during anaesthesia, is often implicated in causing rapidly progressive pulmonary toxicity in patients previously treated with bleomycin.³ These claims have been considered controversial by some, but it is the authors' recommendation that any patient previously exposed to bleomycin therapy should be treated as high risk, and summary guidance regarding oxygen therapy is shown in Table 4.

Bleomycin-induced lung injury typically occurs insidiously during the first 6 months after starting treatment, but the potential for high-inspired fractions of oxygen to provoke pulmonary toxicity remains a life-long risk. All patients who have ever received bleomycin should wear an alert card and an alert sticker should be placed on their notes.

The symptoms of bleomycin-induced pulmonary toxicity are non-specific and include dry cough and breathlessness. Patients may also experience pleuritic chest pain and fever. On examination, pulmonary crackles and hypoxaemia may be found. The diagnosis of bleomycin toxicity must be considered in all respiratory illnesses in patients who have ever received bleomycin.

Bleomycin toxicity has typical appearances radiologically:

- Linear interstitial shadowing may be seen, which can look similar to Kerly B lines seen in pulmonary oedema.
- Confluent airspace shadowing may be present, which may be diagnosed as infection if the diagnosis of bleomycin lung injury is not considered.
- Pneumothorax and pneumomediastinum are recognized complications in severe bleomycin lung injury.

There are particular concerns for patients who are undergoing surgery and who have been treated with bleomycin. Oxygen therapy can both induce and exacerbate bleomycin lung injury. A high concentration of inspired oxygen increases the risk of developing bleomycin-induced lung injury and a lower inspired oxygen concentration reduces the risk. When bleomycin has been administered preoperatively, reduced oxygen concentrations should be used during anaesthesia and postoperatively.³

Pre-assessment of a patient with previous bleomycin exposure will require a thorough history and examination. Depending upon clinical findings, investigations required may include a chest X-ray, arterial blood gases, lung computed tomography, pulmonary function tests, and bronchoscopy. Oxygen should be prescribed on the drug chart, and the dose of oxygen adjusted frequently to maintain

the minimum exposure to achieve a target range of peripheral oxygen saturation between 88% and 92%. If oxygen saturations are higher than this, then oxygen should be stopped or the dose reduced. Ventilatory strategies involving the use of PEEP and careful fluid balance will limit the amount of oxygen required.

Postoperatively, chest physiotherapy, good analgesic regimes, and early mobilization also minimize the requirement for oxygen.

Cardiovascular system

Cardiac toxicity secondary to chemotherapy is common and may be life threatening, cause significant morbidities, or necessitate a change in treatment. The pathologies encountered include hypotension, hypertension, arrhythmias, myocardial infarction, congestive cardiac failure, cardiomyopathy, myocarditis, and pericarditis, leading to pericardial effusion and cardiac tamponade. Cardiac toxicity can be immediate or delayed, after completion of the course of chemotherapy.

Numerous chemotherapy drugs cause Torsades de Pointes, including cisplatin and anthracyclines (including epirubicin and doxorubicin). This results from QT prolongation and may terminate spontaneously, or may lead to ventricular tachycardia and possibly death. Management would be as for any other cause of the arrhythmia. The anthracyclines are the most common drugs implicated in cardiac toxicity, but other drugs such as cyclophosphamide, 5-fluorouracil (5-FU), bleomycin, paclitaxel, and docetaxel can also cause serious cardiac toxicity. There are lots of gaps in the data regarding cardiac toxicity and chemotherapy drugs. Most data are in the form of case series. Chemotherapy drugs tend to damage myocytes, and as there is very little mitosis beyond early adulthood, the heart has to functionally adapt to change, for example, ejection fraction may be preserved but there is decreased cardiac reserve. Radiotherapy may be used alongside chemotherapy and it may cause damage to cardiac valves, vessels, and the pericardium.⁴

The mechanism by which anthracyclines cause cardiac damage is multifactorial but includes production of free radicals leading to apoptosis of myocytes and, subsequently, acute and irreversible cardiac damage. Damage can be severe and life threatening. Clinical signs, however, are late, usually after 12 months or more, by which time it is too late to alter management. Cardiology opinion should be considered as angiotensin-converting enzyme inhibitors can be used to improve ejection fraction.

Cyclophosphamide causes direct endothelial damage and haemorrhagic pericarditis or myocarditis. 5-FU was previously thought to cause acute coronary spasm, but recent evidence suggests that this drug too probably causes myocyte toxicity, which is unpredictable in nature except for an increased frequency in patients with a history of ischaemic heart disease.

Risk factors for cardiotoxicity include pre-existing cardiac disease, the use of concurrent chemotherapy agents, age over 70 yr, female gender, and current or previous radiation therapy involving the mediastinum.⁵ New evidence also shows that at 30 yr after chemotherapy administration, there is an eight- to nine-fold additional mortality from cardiovascular disease in childhood cancer

groups.⁶ Dexrazoxane has been used as a cardioprotective agent but is associated with an increased incidence of secondary malignancies.

When assessing a patient for theatre who has received chemotherapy, the anaesthetist should be mindful of the potential cardiac complications. A focused history and examination, looking specifically for signs and symptoms of cardiac dysfunction, should be obtained. Apart from the routine perioperative investigations, an ECG and a 2D echocardiogram should be requested. The echocardiogram should focus on specific details regarding cardiac wall contractility, left ventricular ejection fraction, and pericardial fluid. If necessary, the patient should be referred for cardiology review for optimization before surgery.

The anaesthetic plan intraoperatively will depend upon preoperative findings. The myocardial depressant effect of the commonly used anaesthetic agents may be compounded by the previous exposure to chemotherapy agents, even in patients with apparently normal cardiac function. As a consequence, all these patients should be treated as high risk for potential cardiac events during anaesthesia. Invasive arterial pressure and cardiac output monitoring will often be necessary to maintain normal physiological parameters. ECG alarm limits should be carefully selected to alert the anaesthetist to any changes in electrical activity within the heart. Normothermia should be maintained using forced air warming devices and warmed fluids. This care should be maintained into the postoperative phase, when careful monitoring in a high dependency unit may be necessary.

Renal system

Several chemotherapy drugs are nephrotoxic, causing either acute or chronic renal failure (Table 3). The platinum-based chemotherapy agents cisplatin, carboplatin, and oxaliplatin, used to treat a huge number of cancers including the lung, upper and lower GI, ovarian, and germ cell tumours, are a common cause of renal tubular and glomerular damage, which can be treatment-limiting. Subsequently, these patients have a long-term higher incidence of hypertension leading to cardiovascular pathology. Ifosfamide can cause a proximal tubular abnormality, cyclophosphamide can cause haemorrhagic cystitis, and mitomycin C is associated with a syndrome encompassing microangiopathic haemolytic anaemia and renal failure.⁷

Of particular importance to the anaesthetist is the knowledge that the nephrotoxic process is compounded by dehydration and concurrent use of non-steroidal anti-inflammatory drugs. Careful fluid optimization and analgesic prescribing is imperative in the perioperative phase.

Nervous system

Chemotherapy may damage any part of the human nervous system. The most common agents with neurotoxic side-effects of significance to the anaesthetist are vincristine and cisplatin.

The vinca alkaloid vincristine can cause severe neurotoxicity. It may be used to treat lymphoma and leukaemia. Vincristine can

cause peripheral neuropathy, muscle pain, cranial neuropathy, and seizures. Of particular concern to the anaesthetist are the effects on the autonomic nervous system, with the development of orthostatic hypotension, and the rare but serious condition of vocal cord palsy.⁸ Vincristine may also exacerbate pre-existing neurological conditions. High-dose methotrexate is used to treat, among other cancers, bone sarcomas and may induce acute encephalopathy, encompassing confusion, seizures, hemiparesis, and coma (usually reversible). Ifosfamide also classically causes encephalopathy, especially in female patients with large pelvic tumours. Paclitaxel and oxaliplatin commonly cause peripheral neuropathy.

Preoperatively, a full neurological examination should be conducted and documented to detect any neurological damage. Regional anaesthesia is relatively contraindicated in any patient demonstrating neurological side-effects after chemotherapy treatment, and, if attempted, careful documentation of deficit before anaesthesia is pertinent.

Gastrointestinal system

Gastrointestinal toxicity is common after administration of most chemotherapy drugs and includes nausea and vomiting, mucositis, and diarrhoea. Not surprisingly, dehydration may occur. In these cases, fluid and electrolyte resuscitation before surgery will be indicated, and rapid sequence induction of anaesthesia to prevent aspiration should be considered.

Direct trauma as a consequence of laryngoscopy will exacerbate the mucositis caused by chemotherapy and can cause severe bleeding leading to difficult visualization of the airway.

Hepatic system

Abnormal liver function tests are a common problem in the cancer patient with possible causes including hepatic metastases, infections, liver disease (e.g. alcoholic liver disease), and hepatotoxic medications. Chemotherapy-related liver damage can also occur, including parenchymal damage with fatty change, cholestasis, and hepatocellular necrosis (Table 3). Methotrexate is known to cause hepatic cirrhosis and fibrosis. Diffuse hepatocellular destruction has been seen secondary to cyclophosphamide treatment.⁹ Many chemotherapy drugs are metabolized by the liver and, as such, require dose reductions if liver function is impaired. Usual precautions for anaesthetic drug dosing in patients with hepatic disease should be applied, and regional anaesthesia may be contraindicated as a consequence of the associated coagulopathy.

Haematopoietic system

Most chemotherapy drugs affect bone marrow and the peripheral blood cells leading to myelosuppression. Life-threatening sepsis and rapid deterioration can occur if a patient develops an infection while neutropenic. Symptoms and signs may not be typical and fever may be absent. Appropriate broad-spectrum antibiotics must be administered immediately, according to local policy. Pancytopenia can have

serious implications for anaesthesia and surgery, causing a reduced oxygen-carrying capacity, an increased risk of haemorrhage and opportunistic infection. A thorough assessment of bone marrow function is imperative before anaesthesia. Consultation with a senior haematologist should be considered. Myelosuppression is usually partially or completely reversible within 6 weeks of cessation of chemotherapy, but in some patients, it may be longer term.

Conclusion

Chemotherapy drugs can produce serious multisystemic side-effects, which directly impinge on the patient's perioperative care. It is the anaesthetist's responsibility to be aware of these potential complications. A thorough preoperative assessment and structured intraoperative and postoperative management plan is required for all patients with a history of previous exposure to chemotherapy agents.

Declaration of interest

None declared.

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Please see multiple choice questions 5–8.