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A practical approach to the patient receiving chemotherapy and anaesthesia

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It is predicted that by the year 2030, South Africa could see the incidence of cancers rise by at least 85%.[1] The ever-increasing incidence of cancer locally and globally, as well as the improved fields of oncotherapy, have increased the frequency of cancer patients presenting for surgery.

Malignancies as a group account for 13% of deaths annually with the commonest sites being lung, colorectal, breast and prostate. Patients with an ongoing malignant process may present for anaesthesia for non-cancer related surgery or for cancer surgery that has an urgency for surgical treatment. While not true emergencies, these patients may not be able to wait a long time for investigations that could delay surgery and allow for cancer spread.[2]

The cancer patient receiving chemotherapy poses numerous challenges at anaesthesia due to deranged systemic physiology, multimodal treatment toxicity and potential drug interactions. The choice of anaesthetic may also have effects on the cancer and its recurrence. As a result, the cancer patient on chemotherapy requires careful consideration. The chemotherapy forms a part of the cancer patients' management but when faced with these patients we have to evaluate them in terms of the tumour effects, the treatment effects and the presence of other comorbidities.[3]

Effects of an ongoing malignant process on the body can be due to:

1. Tumour effects[4]

a. Local effects

b. Hormonal effects

c. Systemic effects

a. Local effects of tumour[5,6,7]

Usually due to four mechanisms:

i. Compression – Seen in mediastinal masses. Patients present with orthopnoea due to airway compression, superior vena cava syndrome which includes facial oedema, distended neck veins, plethora and chest wall vein dilatation, stridor and wheezing. Careful preoperative airway management is mandatory and might even require awake fibre optic intubation or tracheostomy.

ii. Mechanical obstruction – Gastrointestinal tumours can present with an acute abdomen due to intestinal obstruction.

iii. Tissue destruction – Localised destruction and infiltration due to tumour invasion and erosion. Vital structures can be eroded.

iv. Infarction – Results in ulceration and haemorrhage.

b. Hormonal effects of tumour[2,8]

The hormonal effects can manifest from:

- *The primary tumour* – as seen in parathyroid tumours that cause hypercalcaemia, thyroid adenomas that increase thyroid hormones and insulinomas that cause hyperglycaemia. Diabetes mellitus, diabetes insipidus, hypopituitarism and disorders of the adrenal cortex and medulla can also occur.
- *Paraneoplastic syndromes* – Non-metastatic effects that accompany malignancies but may not be directly related. This syndrome is mediated by hormones or cytokines secreted by malignant cells or as an immune response to malignancies usually seen in the elderly with primary tumours of the breast, ovary, lung or lymphatics. Endocrine, neurological, haemotological and mucocutaneous effects have been described.[2]

c. Systemic effects of tumour[2,8]

Multi-systemic dysfunction occurs:

- *Nutritional status*[9] **–** Anorexia, cachexia, weight loss and dehydration all contribute to the disturbed homeostasis of cancer patients. However, benefit of preoperative nutritional support is debatable but has shown promise in head and neck surgery.
- *Pain*[8] – May be due to involvement of somatic nerves, the actual tumour or metastases. Perioperatively the pain these patients experience requires escalation in treatment and cannot be ignored.
- *Depression and distress*[2,9] – Seen in up to 70% of cancer patients and will require the intervention of psychiatric services.

- *Renal failure*[2,10] – Pre-renal failure may occur due to dehydration. An obstructive uropathy secondary to tumours of the bladder, prostate or cervix may also manifest.
- *Infections* – May be due to depressed immunity or interference with bone marrow function.
- *Electrolyte abnormalities*[4] – Any abnormality may exist but be vigilant about hypocalcaemia and hyponatraemia.
- *Haematological effects*[4] – Any of the cell lines can be affected due to myelosuppression and bone infiltration. Two to 10% of patients are prone to thrombosis due to hypercoaguability. It can present as the first sign of an occult malignancy.
- *Cardiopulmonary effects* – Co-existing comorbid cardiac diseases can be exacerbated by malignancies, however, rarely cardiac tamponade or pericardial effusions can present with primary tumours of pericardium or metastases to the pericardium. Pleural effusions and pulmonary fibrosis may also co-exist.[2]

2. Effect of anti-tumour treatment[10,12]

- Radiation
- Chemotherapy
- Targeted therapies
- Bioimmunotherapy
- Stem cell transplantation

Chemotherapy can be adjuvant, neoadjuvant or palliative.

Treatment-related toxicities are common amongst cancer patients and can lead to poor clinical outcomes, a decreased quality of life and increased anaesthetic risk.

Traditional multimodal treatment of tumours includes conventional chemotherapy, radiation and newer targeted therapies. Conventional chemotherapy is highly toxic to the proliferating population of malignant cells as well as organ systems. Radiation is a bit more specific and works in a mapped-out area. Newer modalities in the field of bioimmunotherapy and targeted therapies are more precise in their mode of action with decreased systemic toxicity and an improved side-effect profile.

Radiation therapy is part of multimodal treatment or can be used individually as part of cure or palliation. Effects are dose-dependent. Of concern to the anaesthetist are airway, pulmonary and cardiac effects of radiation therapy.

Radiation to the head and neck region causes soft tissue oedema and bleeding as well as contractures, fibrosis and limited jaw movement. Immobility of the cervical spine and rigidity of the trachea can also be present. Conventional airway techniques might pose difficult and fibre optic intubation can result in haemorrhage due to airway friability. Therefore, mandatory airway management and experienced hands are essential.

Radiation pneumonitis and pulmonary fibrosis with resultant decreased lung compliance and ventilatory difficulty may also occur.[3,4,11] Pericarditis and myocardial fibrosis can present which can affect cardiac contractility and cardiac conduction.[10]

Chemotherapy agents are intended to selectively destroy malignant cells by interfering with a metabolic pathway not present in normal cells.[10,11,12] Thus, systemic dysfunction occurs.

Systemic effects relevant to anaesthesia

1. *Pulmonary toxicity* – Mainly with bleomycin but also seen with cyclophosphamide, nitrosoureas, mitomycin, busulphan and methotrexate. A varied picture presents clinically from a simple cough to bronchospasm, pleural effusions and pulmonary fibrosis.[12] **Bleomycin induced pulmonary fibrosis** is seen in 6–10% of patients. Risk factors include cigarette smoking, advanced age, doses greater than 400 units, previous radiation exposure and lung metastases.[14] If oxygen is being administered to these patients, accept saturation levels of 88–92% and avoid high inspired FiO2 as this accelerates pulmonary toxicity.
2. *Cardiotoxicity* – Mainly with the cytotoxic antibiotics doxorubicin and daunorubicin but also seen with paclitaxel and docetaxel.[10,12] The clinical spectrum includes hypotension, hypertension, arrhythmias, cardiac failure, cardiomyopathies, myocardial fibrosis, arrythmias, myocarditis, ischaemia, infarction and pericarditis. Risk factors include age above 70 years, females and previous radiation exposure. The presence of co-existing cardiac disease, total dose of drug given and presence of other chemotherapy agents increases the likelihood of cardiac complications. These patients will need further cardiac investigations which need to be individualised for each patient.[12,13]
3. *Tumour lysis syndrome* – Seen with cytotoxic chemotherapy agents and present with metabolic derangement causing hyperuricaemia, hypocalcaemia, hyperkalaemia and uraemia. Associated malignancies include leukaemia, small cell carcinoma of the lung, testicular cancer and breast cancer.[2]
4. *Renal effects* – Dose-dependent renal toxicity can occur. Drugs commonly implicated include ifosfamide, cisplatin and carboplatin. Glomerular and tubular dysfunction presenting as non-oliguric renal failure also occurs.[10]
5. *Neurotoxicity* – Methotrexate, vincristine and 5-fluorouracil are neurotoxic. Peripheral neuropathies are common and especially seen in cisplatin where toxicity severity is dose-dependent.[10]
6. *Haematological toxicity* – A pancytopaenia or any single cell line can be affected, with either neutropenia, anaemia or thrombocytopenia.
7. *Gastrointestinal toxicity* – May have anorexia, mucositis, stomatatis, or severe nausea, vomiting and diarrhoea.[10]
8. *Hepatotoxicity* – The liver may also be affected and ranges from mild increases in liver function to fatty liver, cholestasis, cholangitis and life-threatening hepatic necrosis. Drug metabolism can be affected due to hepatic disturbances. Cytochrome P450 enzymes are inhibited by drugs like docetaxel, cyclophosphamide, ifosfamide and vinblastine. Thus, a wide array of drug interactions may occur and can exacerbate toxicity.

1. Commonly used chemotherapy agents[10-13]

Table I highlights the class of drug with a few examples of drugs used, their mechanism of action and the organs affected by these drugs.

Table I. Class of drug with examples of drugs used, their mechanism of action and the organs affected

Class of drug	Mechanism of action	Side-effects	Organ affected/toxicity
Alkylating agents • Cyclophosphamide • Melphalan • Busulfan • Ifosfamide	• Cytotoxic • Alkylates nucleic acids	• increased purines and pyramidines • Uric acid formation • Bone marrow suppression • Pulmonary fibrosis	• Bladder • Renal • Cardiac • Respiratory • Neurological • Git
Antimetabolites • Methotrexate • Mercaptopurines • 5-Fluorouracil	• Cell function affected • Nucleic acid synthetase inhibited • Inhibits purines and pyrimidines	• Bone marrow suppression	• Musculoskeletal • Git • Renal • Respiratory • Haematological
Natural products/vinca alkaloids • Vincristine • Vinblastine • Docetaxel	• Binds to micro tubular protein causing mitotic arrest	• Autonomic neuropathy • Motor neuropathy • Pancytopaenia	• Neurological • Musculoskeletal • Cardiac • Respiratory • Skin
Cytotoxic antibiotics • Bleomycin • Doxorubicin • Daunorubicin • Mitomycin	• Inhibit Dna or Rna or both Dna and Rna synthesis	• Pulmonary fibrosis • Cardiotoxic • Hypersensitivity	• Respiratory • Cardiac
Platinum analogues • Carboplatin • Cisplatin • Oxaliplatin	• Nonspecific cell phase inhibitors	• Ototoxic • Nephrotoxic • Bone marrow suppression • Hypomagnesaemia	• Neurological • Renal • Hepatic • Haematological
New: Bioimmuno-therapy • Interferons • Interleukins • Vaccines • Monoclonal antibodies • Gene therapy • Haemopoeitic growth factor • Hormones-tamoxifen	• Specific targeted therapies	Minimal side-effects: • Flu, fever, myalgia • Constitutional symptoms • Dose Dependent	Minimal organ toxicity
Corticosteroids • May need perioperative supplementation	Induces apoptosis • Used as anti-emetic • Immunosuppressive		

Anaesthetic considerations in patients on chemotherapy

Preoperative evaluation

Due to the complex interplay of physiological, pharmacological and surgical factors, a thorough preoperative assessment is mandatory and must encompass the following:

1. *Type of patient* – Presence of comorbidities, medication history and physical status with risk stratification.
2. *Type of tumour* – Local, systemic and hormonal effects as described.
3. *Type of treatment* – Nonspecific chemotherapy, radiation and newer targeted treatments as described.
4. *Type of surgery* – Non-tumour-related elective surgery, emergency surgery, or tumour-related urgent surgery.

Each patient is individualised based on history, examination and a review of systemic involvement as mentioned. Informed consent must be obtained before proceeding.

The anticipation of airway problems is essential and planning of advanced airway intervention if required. Assessment of cardiopulmonary reserve should prompt a 12 lead electrocardiogram, exercise testing and further invasive testing if necessary.[2,10]

Consideration of nutritional status, pain and psychiatric support is important.

Laboratory investigations should be guided by clinical judgement and may include a full blood count to rule out anaemia, leukopenia and thrombocytopenia. A urea and electrolytes test, liver function tests and coagulation profile might be necessary. If neutropenia exists a strict aseptic technique must be adhered to as infection can be precipitated.

Intraoperative management

Standard ASA monitors are essential, however the need for invasive monitoring including central lines and arterial lines must be individualised to the patient and procedure. Temperature monitoring and the use of forced convection air warmers might be necessary to maintain normothermia.[4] Vascular access might be challenging due to repeated phlebotomy and chemotherapy-induced phlebitis. Precautions need to be taken when positioning these patients with proper padding of pressure points, avoidance of stretch of nerve plexuses and eyes well protected and the abdomen should be free if in the prone position.

Perioperative blood component therapy

Recent controversies surround the use of blood component therapy in cancer patients. Blood has been shown to have immunosuppressive and inflammatory effects. An increased incidence of tumour recurrence with blood transfusions has been suggested in colorectal cancers and hepatocellular carcinomas.[15] However Park, et al. suggest that no prognostic association exists between preoperative blood transfusions and oncology outcomes.[16] Rather, tumour grade, stage or necrosis itself are predictors of poor oncologic outcomes. Platelets and fresh frozen plasma are pro-inflammatory therefore leucodepleted platelet usage has been suggested[17] and limiting blood usage to necessity. 6–8 g/dl has been considered as a threshold for patients without risk factors and 10–11 g/dl in patients with significant risk factors.[2] Thus, blood sparing techniques like maintaining normothermia, antifibrinolytics, preoperative embolisation of highly vascular tumours and maintaining haemodynamic optimisation should be employed.[17] The use of intraoperative cell salvage with malignancies has been causing concern due to a potential for reinfusion of malignant cells at the collection site and increasing the tumour spread systemically.[17] However the use of leucofilters and irradiation have been shown to decrease tumour load of cell salvaged blood.[2]

Choice of anaesthetic technique

Recent debate surrounds general anaesthesia versus regional anaesthesia and its effect on tumour progression. General anaesthesia has been shown to be immunomodulatory and interferes with natural killer (NK) cell activity in animal models when using ketamine or thiopentone.[18] Propofol seems to inhibit tumour progression. Volatiles may promote metastases but minimal clinical data supports this.[19] Regional anaesthesia attenuates immunosuppressive effects of surgery and has a volatile sparing effect thus enhancing perioperative immune function.[19] Retrospective analyses have shown a potential benefit on cancer outcomes with regional techniques in breast and prostate cancers, however prospective randomised control trials are underway in this area. Even if a strong theoretical basis supports the notion that regional anaesthesia can positively affect outcomes after tumour surgery, the actual benefits in practice have not been definitively shown.[18] Thus, perioperative homeostasis should be aimed at maintaining the integrity of immune function and the decision of choice of anaesthetic should be based on type of surgery and patient characteristics.

Amide local anaesthetics in high concentrations are apoptotic and induce cytotoxicity.[20] They also inhibit voltage gated sodium channels (especially ropivicaine) which has a direct inhibitory effect on cancer cells. This has been demonstrated in the treatment of breast cancer cells in rat breast xenografts suggesting local anaesthesia infiltration as ideal in breast cancer surgery.[20] Another promising space to watch is the use of intravenous lignocaine infusions. It is being investigated in mice models as a mechanism to reduce metastatic disease and is showing promise.[21]

Opiates have been thought to suppress NK cell activity, however in vitro animal studies have demonstrated morphine as an inhibitor of apoptosis and a promoter of tumour progression, hence the controversy. Opiates need to be used as part of a balanced anaesthetic. No sufficient evidence exists to stop its use.[18,20]

Nonsteroidal anti-inflammatories (NSAIDs) deserve a special mention as COX2 increases tumour growth and by administering COX2 inhibitors, a decrease in tumour volume has been noted. Data is however limited at this point.[18,20]

Postoperative care

If significant risk factors exist, patients will need to be monitored in a high-care setting.[2] Pain is a major postoperative concern. Perioperatively an acute on chronic pain situation presents itself. Patients on long-term opiate treatment may need escalation from oral to parenteral agents of equivalent doses per hour. Also, be aware of tolerance to drugs due to chronic usage.[2,8,13]

Thromboprophylaxis via mechanical and pharmacological methods needs to be instituted as there is a 45–69% incidence of deep vein thrombosis in cancer patients postoperatively.[2]

Early nutritional support also needs to be instituted and immune enhancing nutrition like glutamine, alanine and omega-3 fatty acids have been shown to decrease infections and inflammation.[9,18]

Conclusion

The cancer patient on chemotherapy has to be assessed holistically. As physiological derangements, tumour effects, treatment toxicities from conventional chemotherapy and newer targeted treatments with less toxicity come to the fore, multiple challenges for anaesthesia exist. As new research develops and the choice of anaesthetic drugs and technique seem to play a role in cancer recurrence outcomes, the role of the anaesthetist in treating these patients intensifies. A multisystemic, multi-disciplinary and individualistic approach is required for these patients so as to maintain perioperative homeostasis and immune function integrity.

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