

Anaesthetic challenges in cancer patients: current therapies and pain management

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The objective. The aim is to present the major effects of cancer treatment (chemotherapy, radiotherapy, surgery) that the anaesthesiologist should consider preoperatively, and to review techniques of the analgesic management of the disease.

Materials and Methods. To summarize the major challenges that cancer patients present for the anaesthesiologists, a literature review was conducted. Articles presenting evidence or reviewing the possible effects of anaesthetics on cancer cells were also included. Online databases of Science Direct, PubMed, and ELSEVIER, as well as reference lists of included studies were searched. Articles published from 2005 to 2016 were selected.

Results. Anaesthesiologists should pay attention to patients receiving chemotherapy and its side effects on organ systems. Bleomycin causes pulmonary damage, anthracyclines are cardiotoxic, and platinum-based chemotherapy agents are nephrotoxic. A lot of chemotherapy agents lead to abnormal liver function, vomiting, diarrhoea, etc. Surgery itself is suspected to be associated with an increased risk of metastasis and recurrence of cancer. Regional anaesthesia and general anaesthesia with propofol should be used and volatile agents should be avoided to prevent cancer patients from perioperative immunosuppression that leads to increased risk of cancer recurrence. Pain management for palliative patients remains a major problem.

Conclusions. To provide the best treatment for cancer patients, cooperation of anaesthesiologists with oncologists and surgeons becomes imperative. It has been established that anaesthetic techniques and drugs could minimize the perioperative inflammation. However, further research of the perioperative “onco-anaesthetic” is needed.

Keywords: anaesthesia, cancer, chemotherapy, radiotherapy, cancer pain

INTRODUCTION

Cancer is a leading health problem worldwide. According to epidemiological data, approximately 40% of people have a chance to develop cancer during their lifetime. Chemotherapy, radiotherapy, and surgery are techniques for cancer treatment with different side effects on the human body. To prepare the best preoperative, intraoperative and postoperative management plans for patients with a history of cancer, the knowledge of long-term and acute side effects caused by these methods of treatment is required of anaesthesiologists. In addition, anaesthesiologists play a major role in the analgesic management of the disease for patients in severe pain (1–3).

A literature review was conducted to summarize the major challenges that cancer patients present to the anaesthesiologists. Articles which presented evidence or reviewed the possible effects of anaesthetics on cancer cells were also included. Keywords such as “current cancer therapies”, “cancer anaesthesia”, “oncologic anaesthesia”, “complications of anti-cancer therapy”, “perioperative”, “cancer surgery”, “propofol cancer”, “immunity”, etc. were used to search databases. Online databases of Science Direct, PubMed, and ELSEVIER, as well as reference lists of included studies were

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CHEMOTHERAPY AND RADIOTHERAPY

Chemotherapy can be neoadjuvant (given before surgery to reduce the tumour size), adjuvant (given during or after surgery), and palliative (given to improve the quality of life). A lot of chemotherapy drugs are anti-proliferative agents targeting rapidly dividing cancer cells. However, non-malignant dividing cells are also affected. Consequently, toxicity of drugs leads to acute and long-term effects on the human organism. The most common toxicities include pulmonary, cardiac, renal, hepatic, and gastrointestinal systems, bone marrow and neurological damage (Table 1). Knowledge of the possible effects of commonly used anti-cancer drugs is necessary for anaesthesiologists to prepare patients with a history of cancer for anaesthesia and surgery (4–6).

Bleomycin is an anti-cancer drug used to treat Hodgkin's disease and germ cell tumours. The worst complication of bleomycin therapy is a subacute pulmonary damage that can progress to pulmonary fibrosis. Faster progression of pulmonary toxicity is associated with an exposure to oxygen therapy of high-inspired concentration

Table 1. Representative chemotherapy agents and perioperative concerns (according to 4, 7)

Organ system	Common perioperative concerns	Associated chemotherapy drugs
Respiratory	Pulmonary oedema	Methotrexate
	Pulmonary fibrosis	Bleomycin, Carmustine, Ifosfamide, Panitumumab
Cardiovascular	Tachycardia	Procarbazine, Cladribine, Alemtuzumab, Trastuzumab, Muromonab-CD3
	Cardiac arrhythmia	Pentostatin, Fludarabine, Palivizumab, Interferon alfa-2b, Erlotinib
	Bradycardia	Docetaxel, Lenalidomide
	Hypotension	Pentostatin, Vincristine, Alemtuzumab, Daclizumab, Muromonab- CD3, Denileukin diftitox
	Hypertension	Pentostatin, Vinblastine, Vincristine, Alemtuzumab, Bevacizumab, Trastuzumab, Daclizumab, Muromonab-CD3, Sorafenib, Sunitinib, Nilotinib
	Cardiomyopathy	Doxorubicin, Trastuzumab, Sunitinib, Dasatinib, Lapatinib
	Renal	Proximal tubular dysfunction
	Hypomagnesemia	Cisplatin, carboplatin
Hepatic	Coagulopathy	Asparaginase
Nervous	Peripheral neuropathy	Vinblastine, vincristine, cisplatin

even for short periods. Therefore, reduced oxygen concentrations should be used during anaesthesia and postoperatively for patients previously treated with bleomycin. Peripheral oxygen saturation should be between 88% and 92%. Moreover, positive end-expiratory pressure (PEEP) ventilation should be chosen (4, 6).

The anthracyclines (epirubicin, doxorubicin) are the drugs implicated in cardiotoxicity. This is the reason why invasive arterial pressure and cardiac output monitoring to maintain normal physiological parameters for patients previously treated with anthracyclines would be necessary (4, 6).

The platinum-based chemotherapy agents (cisplatin, carboplatin, and oxaliplatin) are nephrotoxic. They can cause either acute or chronic renal failure. The nephrotoxic process is augmented by dehydration and concurrent use of non-steroidal anti-inflammatory drugs. Careful fluid optimization and dosage of analgesics are imperative perioperatively (6).

A lot of chemotherapy drugs are metabolized by the liver. Anaesthetic drug dosage must be reduced for patients with an impaired liver function. Regional anesthesia is contraindicated in the cases of the associated coagulopathy (6).

Gastrointestinal toxicity is common after the administration of chemotherapy drugs. Side effects, which include nausea, vomiting, mucositis and diarrhoea, lead to dehydration. In these cases, prescription of fluids and electrolytes is indicated before surgery. Rapid sequence induction of anaesthesia should be considered. Furthermore, it should be known that laryngoscopy may exacerbate the mucositis and lead to severe bleeding (6).

Most chemotherapy drugs affect bone marrow and the peripheral blood cells. It leads to myelosuppression which is usually reversible within six weeks of cessation of chemotherapy. The anaemia as a secondary response of malignant disease is curable without blood transfusion within a period of 2–3 weeks. However, transfusion of blood products may be required in the cases of anaemia caused by myelosuppression and urgent surgery. It should be remembered that anaemia treated with preoperative blood transfusion may recur in the postoperative period. This is the reason why patients should be followed up after surgery. Neutropenia is associated with infections postoperatively. To avoid severe complications, broad-spec-

trum antibiotics must be administered. The use of granulocyte colony-stimulating factors for neutropenic patients who are undergoing surgery is controversial. Platelet transfusion must be balanced against the prothrombotic state that cancer induces for cancer patients with thrombocytopenia. A patient with pancytopenia should be consulted by a haematologist before surgery (4, 6, 7).

The most common agents with neurotoxic side effects are vincristine and cisplatin. The vinca alkaloid vincristine is used to treat lymphoma, leukaemia, and can cause peripheral neuropathy, muscle pain, cranial neuropathy, and seizures. However, the major problems for anaesthesiologists are associated with the effects on the autonomic nervous system: the development of orthostatic hypotension and vocal cord palsy. Preoperatively, a full neurological examination to detect any neurological damage should be conducted (5, 6).

Chemotherapy drugs are frequently combined in various ways, which causes multiple side effects. Furthermore, commonly used drugs continued during anaesthesia may inactivate anti-cancer drugs or lead to an increased risk of bleeding (Table 2) (4, 5, 8).

Radiotherapy is frequently used in combination with chemotherapy. Chemoradiation for oesophageal, pulmonary, cervical, head and neck, rectal and urinary bladder cancers can be used to achieve a complete anti-tumour response. Radiotherapy causes tissue damage through the production of oxygen-free radicals. As a consequence, they can cause delayed wound healing, induration of the skin, vascular stenosis, myocarditis, pneumonitis, and pulmonary fibrosis. Anaesthesiologists are faced with the challenge of management of patients with head and neck cancer. Airway management of these patients is difficult because of the site and size of the tumour. Previous treatment with radiotherapy could also lead to a limited neck extension and rigidity of the oropharyngeal tissues. This makes ventilation with a face mask and laryngoscopy difficult. Radiotherapy for the head and neck leads to a difficult central venous access. Therefore, in the cases of a long-term treatment with chemotherapy, a central or peripherally inserted central venous catheter is frequently needed. Furthermore, mucositis as a consequence of radiotherapy can be exacerbated by tracheal intubation (1, 5, 6, 9, 10).

Table 2. Common medications and possible interaction with anti-cancer medications [according to 5]

Medication	Chemotherapy medication	Subsequence
Warfarin	Fluorouracil/capecitabine/ carboplatin/etoposide/ paclitaxel/gemcitabine	Higher risk of bleeding
Ondansetron	Cisplatin	Reduced plasma concentration of cisplatin
Phenytoin	Fluorouracil	Plasma phenytoin concentration may be elevated
Cimetidine	Fluorouracil	Increased plasma concentration of fluorouracil
Furosemide	Cisplatin	Additive ototoxicity
Ketoconazole	Proton pump inhibitors	Decreased ketoconazole absorption
Hydrochlorothiazide	Cyclophosphamide/fluorouracil	Possible prolonged chemotherapy induced neutropenia
Acetaminophen	Imatinib	Acetaminophen breakdown may be reduced

Chemotherapy and radiotherapy have a broad range of complications and toxicity. Therefore, preoperative assessment to identify any side effects of treatment, as well as structured intraoperative and postoperative management plans, is required for all patients with a history of cancer. The interval between the end of neoadjuvant chemotherapy and surgery depends on the type of cancer. A treatment plan aimed at choosing the best interval for surgery to avoid acute side effects of chemotherapy should be discussed with oncologists. For example, myelosuppression, coagulation disorders, renal or hepatic impairment, or anaphylactic reactions may develop unexpectedly.

SURGERY AND ANAESTHETIC TECHNIQUES

Surgery is a method of cancer treatment used frequently. Surgery is also performed for preventive, diagnostic, staging, debulking, supportive, and palliative purposes. A major cancer surgery has an influence on neuroendocrine (the hypothalamic–pituitary axis, the sympathetic nervous system) and cytokine-mediated stress responses followed by immunosuppression. Furthermore, circulating tumour cells are released and tumour emboli are disseminated during surgery. This is the reason, why surgery itself is suspected to be associated with an increased risk of metastasis and recurrence of cancer. Several studies have suggested that perioperative anaesthetic, analgesic techniques, and drugs may affect a postoperative inflammation and the immune function (2, 3, 11).

Regional anaesthesia and analgesia may influence cancer recurrence. Lidocaine and bupivacaine inhibit transcription pathways associated with the initiation and metastasis of cancer and with decreased mesenchymal stem-cell proliferation. The use of regional anaesthesia, especially thoracic epidural analgesia, has a variety of benefits for patients postoperatively: improved analgesia as well as reduction of opioids-associated side effects, inflammatory response and adrenergic response to increased circulating catecholamine levels, factors believed to be mediating postoperative immune suppression. Regional anaesthesia may increase the expression of several cytokines expressed perioperatively, including IL-4 and IL-10, which may directly or indirectly attenuate the surgery-induced proinflammatory response and reduce the rate of postoperative complications. Alternatively, local anaesthetics may directly stimulate natural killer cells (NK-cell) activity. NK-cells are important in the destruction of tumour cells. Local anaesthetics are suggested to have anti-proliferative and cytotoxic effects on cancer cells (3, 11).

Volatile agents are associated with immune modulation and potentially increase the ability of tumour metastasis. The possible mechanisms are decrease of NK-cell activity, interference with lymphocyte antigen activity, and induction of apoptosis in T-lymphocytes and in B-lymphocytes. Furthermore, volatile agents may have direct effects on cancer cells (12, 13).

Non-volatile agents such as non-volatile anaesthetic gas nitrous oxide (N₂O) and the intravenous anaesthetic agents (ketamine, thiopentone, propofol) are being investigated for their immune

modulating effects and potential effects on cancer recurrence. It was determined in the studies that low-dose ketamine suppresses NK-cell cytotoxicity and inhibits the production of pro-inflammatory cytokines (IL-6 and TNF- α). As a consequence, immune suppression is associated with the recurrence of cancer. However, propofol may have an anticancer effect. Different studies made *in vitro* established a lot of mechanisms how propofol acts as an anticancer agent: it inhibits tumour size, cell viability, induces cell apoptosis, or inhibits invasion and angiogenesis of cancer (14–17).

Opioids have different effects on the immune response and the reason is unclear. The pathways of endogenous opioids are thought to induce anticancer effects whereas exogenous opioids are believed to have pro-cancer effects. Endorphin increases NK-cells cytotoxicity and favours anti-inflammatory cytokines. Therefore endorphin has been considered as a possible anticancer therapeutic agent. Exogenous opioids suppress the immune function. They inhibit humoral and cell-mediated immune functions and increase tumour growth rate (3).

To conclude, general anaesthetics do not cause the development of cancer directly. However, immune suppression induced by anaesthesia could lead to a faster progress of cancer. On the contrary, regional anaesthesia and anaesthetic induction with propofol are associated with the prevention or reduction of perioperative immunosuppression. Larger prospective studies to determine the role of anaesthetic techniques for prevention of tumour recurrence or metastasising are required (18–20).

PHARMACOLOGICAL MANAGEMENT OF CANCER PAIN

Severe cancer pain, which does not seem to be relieved using the three-step “pain ladder” method (step 1 being employed for the treatment of mild cancer pain with non-opioid analgesia, step 2 for moderate pain with “weak” opioids and step 3 for severe pain with “strong” opioids), is uncommon but can occur in up to 10% of patients. In those patients, interventional pain management techniques, including simple local anaesthetic blocks, possibly maintained for a prolonged term by insertion of peripheral nerve catheters, as well as techniques of neuraxial analgesia and, finally, neurodestructive techniques may be considered (21).

Nerve blocks. Myofascial trigger point infiltrations may be useful in some patients. Otherwise, peripheral nerve blocks can provide short-term relief in acute situations, for example, before surgical repair of a pathological fracture. In the cases of a terminal situation with pathological fractures, catheters to peripheral neural structures and continuous infusions of local anaesthetic can provide a management option for days or weeks (22).

Neuraxial analgesia. The most widely accepted method is the insertion of an intrathecal catheter with continuous administration of opioids, commonly combined with local anesthetics and other adjuvants, particularly clonidine. It is possible to use percutaneous catheters connected to external pumps for weeks and months provided that strict asepsis and excellent care are applied (19).

Neurodestructive procedures. Neurodestructive procedures can be performed with the use of neurolytic agents as well as with the application of excessive temperatures by radiofrequency or cryoneurolysis. Percutaneous chordotomy is the destruction of the spinothalamic tract, made usually by radio frequency lesioning. It could be used to treat unilateral pain on the opposite side (23).

Neurolytic sympathetic blocks. For the treatment of pain originating from upper abdominal cancers the most and best experience is available with coeliac plexus neurolysis, especially in cases of the pancreatic cancer. An alternative technique is the neurolysis of the splanchnic nerves. Neurolytic procedures to the superior hypogastric plexus or to the lumbar sympathetic chain addressing pain originating from the lower abdomen and the pelvis could be used successfully. Another sympathetic neurolytic block is that of the ganglion impar, the terminal bit of the sympathetic chain. It is used for the treatment of pain originating from the prostatic or rectal cancer (24).

Terminal sedation. Even at the end of life, pain can usually be controlled with continuation of opioids, using the subcutaneous route if needed. When death is near, these symptoms and/or refractory pain may require to be managed with palliative sedation (21).

CONCLUSIONS

Currently, cancer is a leading health problem worldwide. To provide the best treatment to cancer patients, cooperation of anaesthesiologists with oncologists and surgeons becomes imperative. It

is obvious that radiochemotherapy and surgery are important in the treatment of cancer, and anaesthesiology facilitates their advance. However, treatment techniques may have significant acute and long-term side effects on the human body. Therefore preoperative assessment to identify any side effects from the treatment, structured intraoperative and postoperative management plan are required for all patients with a history of cancer. It is established that anaesthetic techniques and drugs could minimize perioperative inflammatory and immune changes. Apparently, this could lead to better outcomes for cancer patients in the future. However, further research into perioperative “onco-anesthetic” and perioperative cancer medicine is needed.

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ONKOLOGINIŲ PACIENTŲ ANESTEZIOLOGIJOS PROBLEMOS: ŠIUOLAIKINIAI GYDYMO BŪDAI IR SKAUSMO VALDYMAS

Santrauka

Tikslas. Pristatyti vėžio gydymo būdų (chemoterapijos, radioterapijos, operacinio gydymo) šalutinius poveikius, kuriuos anesteziologas turėtų apsvarstyti prieš operaciją, ir apžvelgti skausmo valdymo technikas.

Metodika. Literatūros apžvalga atlikta siekiant apibendrinti pagrindinius iššūkius, tenkančius anesteziolo-

logui, gydančiam onkologinius pacientus. Apžvelgiami straipsniai apie galimą anestetikų poveikį vėžinėms ląstelėms. Peržvelgtos viešai prieinamos internetinės duomenų bazės: Science Direct, PubMed, ELSEVIER ir straipsniuose pateikti literatūros šaltiniai. Atrinkti 2005–2016 m. publikuoti straipsniai.

Rezultatai. Anesteziologai turėtų atkreipti dėmesį į pacientus, kuriems paskirtas chemoterapinis gydymo būdas, taip pat šio gydymo sukeltus šalutinius poveikius organų sistemoms. Bleomicinas pažeidžia plaučius, antraciklinai yra kardiotoksiški, platinos chemopreparatai – nefrotoksiški. Daug chemopreparatų sukelia kepenų funkcijos sutrikimus, vėmimą, viduriavimą ir kt. Įtariama, kad operacinis gydymas susijęs su padidėjusia metastazavimo ir vėžio atsinaujinimo rizika. Siekiant apsaugoti pacientus nuo pooperacinės imunosupresijos, turinčios įtakos vėžio atsinaujinimui, rekomenduojama regioninė anestezija ir bendroji anestezija propofoliu, o garinių anestetikų reikėtų vengti. Paliatyviojo gydymo pacientų skausmo valdymas išlieka didele problema.

Išvados. Siekiant suteikti geriausią gydymą onkologiniams pacientams, anesteziologų bendradarbiavimas su onkologais ir chirurgais yra neišvengiamas. Nustatyta, kad anesteziologinės procedūros ir vaistai gali sumažinti operacijos metu sukeltą uždegimą. Reikalingi tolimesni optimalaus „onkoanestetiko“ paieškų tyrimai.

Raktažodžiai: anestezija, vėžys, chemoterapija, radioterapija, vėžinis onkologinis skausmas