Review Article

Neo-adjuvant chemotherapy and its anaesthetic implications for surgery—a narrative review

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Objective: To review and summarise the current literature describing the effects of neo-adjuvant chemotherapy on the body's main organ systems and the subsequent anaesthetic implications of these changes in patients undergoing major oncological surgery. To offer a summary of evidence-based multidisciplinary-led solutions in order to mitigate these impacts.

Background: Chemotherapy when delivered prior to surgery, termed neoadjuvant chemotherapy (NAC), has an invaluable role in the management of many cancers by decreasing tumour burden and allowing surgical management of otherwise unresectable tumours. Chemotherapy however also causes damage to healthy cells, and subsequently affects all main organ systems, and potentially reduces cardiopulmonary reserve.

Methods: Narrative overview of the literature summarising the existing evidence base in this field, retrieved from computerised database searches, authoritative websites and journals.

Conclusions: A summary of the effects of NAC on the cardiovascular, respiratory, renal, neurological, hepatic, haematological, musculoskeletal and gastrointestinal systems is discussed along with the anaesthetic implications of these. Furthermore, the effect of NAC on cardiopulmonary reserve is reviewed. Potential methods by which these impacts can be mitigated by the well-informed anaesthetist alongside the rest of the multidisciplinary team are outlined. Knowledge and understanding of the physiological derangements caused by NAC, allows the multidisciplinary team to alleviate these negative impacts. Optimal timing of surgical intervention, prehabilitation programmes and optimisation of organ systems are some interventions which may give these complex high risk patients the best possible outcomes.

Keywords: Anaesthesia; surgery; cancer

Received: 19 March 2021; Accepted: 28 June 2021; Published: 30 September 2021.

doi: 10.21037/dmr-21-29

View this article at: https://dx.doi.org/10.21037/dmr-21-29

Introduction

Cancer remains a leading cause of death worldwide. An estimated 9.6 million deaths were attributable to cancer in 2018, according to data from the World Health Organisation (1).

Historically, surgical resection of tumour was the mainstay of treatment for many cancers (2). Anti-cancer therapies, including chemotherapy, have been introduced as

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Table 1 Sources used for this overview

GOOGLE SCHOLAR and PubMed search: 1950–January 2021. Key words: Neoadjuvant chemotherapy, Systemic effects, Cardiopulmonary reserve, Anaesthetic implications
PubMed 'related articles' tool from identified papers of interest
Hand searches of the references of relevant literature
Hospital library searches for texts on neoadjuvant chemotherapy and anaesthetic implications

adjuncts allowing for less radical surgical approaches with improved outcomes (3). Chemotherapeutic agents target rapidly dividing cancer cells through anti-proliferative actions, stimulating cancer cell apoptosis. Chemotherapy thus has a versatile role within many cancer treatment regimes. Its main uses can be summarised as: neoadjuvant (given prior to surgery in order to reduce tumour size), adjuvant (given during or after surgery in order to reduce the risk of cancer recurrence) or palliative (where there is no curative intent, but it is used to prolong survival or improve quality of life).

Neoadjuvant chemotherapy (NAC) is used in the treatment of a number of malignancies of the digestive tract, including colorectal, gastric, pancreatic and oesophageal cancers, but is also used prior to surgery for lung, prostate, ovarian, breast and cervical cancers (4). A survival benefit from NAC in patients undergoing oesophagogastric surgery has been repeatedly demonstrated (5-7). In those with hepatic metastases of colorectal cancer, NAC may be used to decrease the tumour burden and allow previously unresectable disease to be operated on. In this group, there is evidence to suggest that NAC is not associated with poorer outcomes (8), although concerns exist regarding systemic effects.

The use of chemotherapy agents is limited by their systemic effects. Their anti-proliferative actions also affect 'normal' host cells, leading to drug toxicity and detrimental physiological effects. 'Cycles' of chemotherapy are therefore often used, allowing a period of recovery between periods of treatment. Cycles usually span 2–3 weeks and full chemotherapy regimens can span months to years. To minimise toxicity of chemotherapy agents, combination chemotherapy is often utilised whereby agents with differing mechanisms of action are administered together. This increases the proportion of cancer cells eliminated due to synergistic drug effects, as well as reducing the likelihood of resistance developing to a single agent modality. The toxicity of chemotherapy drugs is related to many factors including: the specific agents used, their cumulative dosage, cross-reactivity between agents, as well as patient factors including pre-existing comorbidities.

With improvements in management strategies for patients with cancer, we may encounter increasing numbers of such patients undergoing both elective and emergency surgery. Moreover, with an increase in use of NAC as well as other adjunctive treatments for cancer treatment, many patients will be approaching surgical procedures following exposure to their potentially toxic systemic effects. It is therefore imperative to the anaesthetist to know how patient physiology is affected by chemotherapeutic agents and how peri-operative anaesthetic management must be adapted accordingly. Furthermore, growing concerns that the harmful effects of in NAC may result in poorer perioperative outcomes for some (5) mandate that we engage robust shared decision-making.

This review will consider the systemic effects of chemotherapy agents and how we can seek to overcome these challenges in our role and as part of the wider multidisciplinary team (MDT). We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/dmr-21-29).

Methods

Table 1 outlines the sources of information used to write this paper.

Systemic effects of chemotherapy

Cardiovascular system

The cardiovascular system is relatively vulnerable to chemotherapy-related damage, and with minimal mitotic activity of cardiac myocytes after early adulthood, such damage cannot easily be reversed. Cardiovascular complications (including cardiomyopathy, arrhythmias, myocardial infarction, hypertension, etc.) are perhaps the most commonly recognized adverse effects of chemotherapy in the short and medium term (9-12) and may go on to be the leading cause of death in cancer survivors in the long term (13). The cardiovascular effect of chemotherapeutic agents is a vast topic and to go into detail is beyond the scope of this narrative review, however a brief overview is included below. A 2016 position paper from The Task Force for cancer treatments and cardiovascular toxicity

of the European Society of Cardiology (9) gives an expert overview, and there have been comprehensive narrative reviews written on the subject to which the reader is directed (14).

Anthracyclines have widespread and longstanding use as chemotherapy agents and their cardiotoxic effects are well described, particularly with respect to heart failure. Anthracycline-related heart failure can occur early (within a year) but also much later (9,15,16). Multiple other agents including cyclophosphamide, the taxanes (including paclitaxel and docetaxel), 5-fluorouracil (5-FU) and tyrosine kinase inhibitors are hazardous to cardiomyocytes via alternative cardio-toxic mechanisms.

Historically chemotherapy-related cardiotoxicity was classified according to the underlying mechanism of drug-mediated toxicity, however this has been debated recently (17,18). Type 1 cardiotoxicity describes anthracycline driven myocyte damage, and also includes cardiotoxicity due to other drugs such as mitoxantrone. The underlying pathophysiological process is multifactorial including myocyte damage secondary to reactive oxygen species that may be exacerbated by pre-existing individual genetic venerability or underlying cardiac dysfunction. It is a cumulative dose-dependent form of cardiotoxicity and once myocyte death has occurred, cell regeneration is limited and so this form of cardiotoxicity is largely irreversible. Chronically following anthracycline exposure, while overall cardiac function may be preserved by functional adaptation (which can be aided through pharmacological optimisation) there will still be a loss of cardiac reserve (13,19), and an increased likelihood of congestive cardiac failure.

Type II cardiotoxicity results from exposure to tyrosine kinase inhibitors and other monoclonal antibody drug agents (13,20). They transiently impair myocyte function and therefore can also cause cardiac dysfunction, but unlike type 1 toxicity there is restoration of cardiac function following cessation of the perpetrating agent (13,19). Patients may display a mildly reduced ejection fraction but are often asymptomatic and in general repeated dosing of such drugs are well tolerated (13).

Cardiac ischaemia may be provoked by agents used as part of a treatment regime of cancers of the digestive tract, including 5-fluorouracil (5-FU), Capecitabine, Cisplatin, and Vinka Alkaloids (14). The mechanism may include vasospasm or thrombosis, as well as longer-term changes promoting arteriosclerosis (9), and there may be unmasking of underlying coronary artery disease (14).

Arrythmias may occur after chemotherapy, and this may include the perioperative period. The acute cardiotoxicity that can be precipitated by anthracycline therapy normally takes the form of conduction defects (9,21). QT prolongation may occur and this can precipitate a range of arrhythmias including Torsade de Pointes or other ventricular arrhythmias which can lead to sudden death (22). Cisplatin may contribute to arrythmias via its effect on the renal system and subsequent electrolyte disturbances (14). The taxanes may cause AV or LBB block but may also lead to VT (14).

Valvular heart disease is unlikely to be caused by chemotherapy but may be present in patients presenting for surgery having received NAC for related reasons (including radiotherapy) (9).

Those at increased risk of cardiotoxicity include patients with pre-existing heart disease, concurrent use of radiotherapy or multiple cardio-toxic chemotherapy agents, age > 65years and female gender (9).

Respiratory system

Pulmonary toxicity is associated with a number of agents including bleomycin, methotrexate, cyclophosphamide, mitomycin and busulfan. There is limited understanding of the pathophysiological mechanisms underlying drug induced pulmonary toxicity and they are likely multifactorial. Alveolar and bronchial epithelial cells may be directly damaged by exposure to chemotherapy agents, which coupled with a deranged immunological response may result in chronic inflammation and subsequent fibrosis (23,24). Pulmonary oedema may result from arabinoside and bleomycin use (25), and methotrexate may result in pleural effusion (25) and progressive pulmonary fibrosis (22,26). Possible risk factors for the development of pulmonary toxicity in patients undergoing chemotherapy include pre-existing lung disease, thoracic radiotherapy and a history of smoking.

The immunosuppressive effects of chemotherapy leave patients at increased risk of lower respiratory tract infection (22).

There is limited evidence regarding the respiratory effects of NAC treatment in the immediate perioperative period. A recent paper found in those undergoing NAC for breast cancer there was a significant reduction in the diffusing capacity for carbon monoxide (DLCO) and postulated that this was a logical consequence of the above pathological changes in the lung parenchyma which would increase diffusion distances (27). These findings were

mirrored in another study where a statistically significant reduction in DLCO was seen in patients undergoing NAC for treatment of non-small cell lung cancer (NSCLC) although interestingly there was no increase in post-operative pulmonary complications (28). A retrospective analysis of over 50,000 patients that had undergone anastomotic lung resections, found no difference in 30-day mortality rates between patients that received neoadjuvant therapy versus those that did not (29).

Bleomycin warrants special consideration from an anaesthetic perspective. Although predominantly used in the treatment of Hodgkin's disease and germ cell tumours, it is also employed in a neo-adjuvant role for the management of some gynaecological cancers (30-33). A major limitation to the widespread use of bleomycin is its well-known association to induce lung toxicity, occurring in up to 10% of patients, and with a mortality of 1% (34).

The underlying mechanism of toxicity is likely to be similar to the processes outlined above with direct cytotoxicity from bleomycin exposure causing damage to respiratory epithelial cells potentially resulting in a metaplasia from squamous to cuboidal epithelium. Further exposure prevents reversion of the affected cells and a defective immune response results in macrophage invasion and ultimately an inflammatory picture causing pulmonary fibrosis. It has also been proposed that bleomycin exposure results in the production of free radical moieties which interfere with DNA homeostasis and lead to cell death. The production of these highly oxidising free radicals is said to be vastly accelerated by the presence of increased concentrations of inspired oxygen such as during the process of pre-oxygenation prior to induction of anaesthesia (35).

Renal system

The detrimental effect of chemotherapy agents on renal function is well documented, and methotrexate, ifosphamide and mitomycin may cause acute or chronic renal failure. The acute nephrotoxicity associated with methotrexate is a result of its precipitation within renal tubules resulting in a physical obstruction of renal tubular flow, whereas mitomycin can lead to microangiopathic haemolytic anaemia which can result in chronic renal failure. It is the platinum-based chemotherapy agents (including cisplatin) that are most commonly associated with nephrotoxicity. Approximately 20% of patients exposed to cisplatin will develop nephrotoxicity (36) which often becomes the dose-limiting factor for its single agent use. Coagulation necrosis of tubular epithelial cells within the nephron leads to a reduction in glomerular filtration rate and wasting of electrolytes including potassium and magnesium (36).

Despite these nephrotic effects, cisplatin and related agents are used in the treatment of a large number of cancers including gastrointestinal, ovarian, lung and genitourinary tumours including in a neoadjuvant role. The European Association of Urology guidelines state that there is level 1a evidence to support the use of neoadjuvant cisplatin-containing combination chemotherapy to improve overall survival in certain forms of bladder cancer (37) and trials investigating the impact of NAC in patients undergoing urological surgery for cancer found no clinically significant increase in perioperative complications or morbidity and no clinically significant deterioration in long term renal function (38-41). Moreover, there is even evidence that cisplatin-based therapy is a safe and viable option in managing bladder cancer patients that already have baseline renal dysfunction without exacerbating nephrotoxicity, albeit with specifically tailored NAC regimens (42). Similar findings of non-nephrotoxic NAC regimens (which included cisplatin) have been seen in the management of other cancers as well, including oesophageal (43,44).

Nervous system

The relative incompetence of neuronal tissue to regenerate following damage means neurological sequelae following chemotherapy is commonplace. Up to 40% of patients may experience peripheral neuropathy following chemotherapy (45,46). Its aetiology may include toxic effects on DNA, interference with microtubules or disruption with mitochondria (45).

Cisplatin is another common culprit of neurotoxicity post chemotherapy, causing peripheral neuropathy, loss of tendon reflexes and ataxia (25).

Central neurotoxicity resulting in cerebellar dysfunction, encephalopathy, seizures, hemiparesis and coma have been observed following high doses of methotrexate, ifosphamide, cytarabine and 5-Fluouracil (47).

Autonomic instability may occur following vincristine use (22). The New York School of Regional Anaesthesia warns of autonomic involvement following chemotherapy use (46). It is not clear to what extent any ANS instability affects outcomes in patients, and much of the literature does not account for confounding factors (including other factors

which may contribute to ANS changes) (48).

Hepatic system

Chemotherapy related hepatotoxicity is not uncommon. Up to 85% of patients undergoing chemotherapy may display an element of steatosis due to disturbed lipid metabolism within hepatocytes (49). The increase in hepatocellular lipid content can induce the recruitment of inflammatory cells and lead to hepato-cellular damage characterised in steatohepatitis. Elevation of aminotransferases is a frequent occurrence following chemotherapy and there is impairment of the phagocytic activity of Kuffper cells (49). It is important to bear in mind, that although hepatic dysfunction may be due to chemotherapy related hepatotoxicity, it may also point to infection, increased metastatic burden, decompensated pre-existing liver disease, veno-occlusive disease, toxicity from other medications or paraneoplastic syndromes.

Chemotherapy may be given prior to hepatic resection of colorectal metastases with the aim of improving tumour resectability prior to surgery (50,51). There is an evidence base which demonstrates no increase in complications post NAC-induced steatosis, even when steatosis is severe (52), though there is no firm consensus on this matter. Recent literature reflects a growing concern regarding systemic chemotherapy in this group, specifically regarding irinotecan and oxaliplatin use and subsequent chemotherapy-associated liver injury (CALI) (53-55), as well as chemotherapy-induced acute steatohepatitis (CASH), whose mechanism is due to mitochondrial toxicity and is associated with a number of agents, including those used as NAC in cancers of the digestive tract (methotrexate, 5-fluorouracil, irinotecan, tamoxifen and L-asparaginase) (56). Questions have been raised regarding whether the above impact mortality and morbidity in this group (51,56). Postoperative liver failure increases mortality and morbidity after liver resection (57,58), and questions of whether this chemotherapy-induced liver damage (particularly in the form of NASH) might be associated with poorer liver regeneration (and so poorer outcomes) postoperatively have been raised, though at present there is limited evidence (a systematic review is planned which aims to address this important question (57).

Haematological system

Chemotherapy can cause or contribute to anaemia, thus reducing the oxygen carrying capacity of blood, and the burden increases with ongoing cycles of chemotherapy (59,60). The European Cancer Anaemia Survey (ECAS) demonstrated an increase in terms of anaemic patients from 19.5% to 46.7% between one and five cycles of chemotherapy (61). Platinum-based agents may cause myelosuppression (59,60,62) and the renal toxicity caused by cisplatin may reduce renal erythropoietin production and so contribute further (60,63,64).

Reduced leukocyte production is often the most important hematopoietic impact of the bone marrow suppression associated with the majority of chemotherapy drugs. Leucocyte counts tend to be lowest (the 'nadir') approximately 7–14 days after a cycle of chemotherapy. Infection associated with neutropenia can be life threatening and is commonly poorly diagnosed as typical infective symptoms and signs such as pyrexia may be absent. Fortunately myelosuppression is usually partially or completely resolved 6 weeks post cessation of chemotherapy (22).

Thrombocytopaenia is another common finding in cancer patients and while chemotherapy is one of the causes, it may also be a consequence of radiation treatment, adverse reactions to other medications, infections, other medical co-morbidities, auto-immune responses or the underlying cancer itself. Platinum based regimens and gemcitabine are associated with the highest incidences of thrombocytopenia and the mechanisms by which this is caused is multifactorial (22,65).

Chemotherapy (along with a number of other factors) has been demonstrated to be an independent risk factor for venous thromboembolism, particularly in those undergoing gynaecological-oncological surgery (66-68).

Musculoskeletal and gastro-intestinal systems

A decrease in muscle mass occurring during NAC (particularly for oesophageal cancer) is associated with poorer outcomes (particularly pulmonary, but also all complications) (69).

Chemotherapy agents including Cisplatin may cause nausea and vomiting, as well as mucositis due to the same mechanism as treatments' anticancer agents (targeting the rapid turnover of cells in the GI tract) (70).

NAC, cardiorespiratory fitness, and outcomes

There is an increasing interest in the relationship between

NAC and cardiorespiratory reserve, with an expanding evidence-base.

The relationship between cardiorespiratory fitness and surgical outcome

There is a well-established body of evidence which demonstrates an observed relationship between cardiorespiratory reserve and postoperative outcomes. The beginnings of this lie almost 30 years ago, when Older and colleagues demonstrated that an anaesrobic threshold (AT) greater than or equal to 11 mL/min/kg was associated with a perioperative mortality of 0.8% compared with 18% for those whose AT was below 11 mL/min/kg (71). Older *et al.*'s findings in this seminal paper have been repeatedly replicated over the years, demonstrating an association between AT and both mortality and morbidity, with much of this evidence base relating to patients undergoing major elective abdominal surgery (72-76). As such, cardiopulmonary exercise testing is relatively routinely used to stratify surgical risk pre-operatively, and subsequently help to determine whether surgery is appropriate, and to aid perioperative planning (including post-operative destination).

In terms of evidence to the contrary, a recent study specifically concerning oesophagogastric cancer which found no evidence of an association between AT and outcome, finding no correlation between AT and morbidity at 30 days, although this was a relatively small (254 participants) observational study (77).

The relationship between NAC and reduced AT

The above evidence regarding cardiorespiratory fitness (particularly as determined by AT) is pertinent because of the growing evidence-base which demonstrates a reduction in cardiorespiratory reserve (measured by CPET) in patients who have received NAC. The majority of evidence in this area concerns patients undergoing resection of oesophagogastric carcinoma, and a reduction in AT has been demonstrated both in the period immediately following NAC as well as in the period between treatment and surgical resection (78-80).

The above appears to suggest a potential conflict in our evidence base (at least at the population level). On one hand there is evidence of improved outcomes in certain oncological populations (and of no harm in others) using NAC prior to surgical resection, alongside the implication that if NAC reduces cardiorespiratory reserve, then it may follow that this could result in poorer surgical outcomes, as has been repeatedly demonstrated in the wider surgical population.

To add further evidence into the mix, a 2014 study concerning patients with cancers of the upper gastrointestinal tract found poorer outcomes in terms of postoperative survival in those with poorer baseline physical fitness (determined by CPET) in those who completed a course of NAC prior to surgery, but did not find this relationship in those who did not complete NAC, concluding that (in some patients—possibly those with 'borderline fitness' pre-treatment) the benefits of NAC may be outweighed by the potential harm (5).

Prehabilitation

Multidisciplinary prehabilitation programmes include interventions aimed at optimising patients physiologically and psychologically prior to surgical intervention, and the evidence base supporting their use is expanding (81). The rationale for prehabilitation lies in the presumption that an improvement in functional capacity (including cardiorespiratory reserve) will result in a better ability to withstand the surgical stress response, and so lead to improved outcomes. This is an intuitively appealing concept; particularly given the evidence we have considered regarding anaerobic threshold and surgical outcomes outlined above. A large systematic review and meta-analysis in 2014 found that prehabilitation "improved postoperative pain, length of stay and physical function, but it was not consistently effective in improving health-related quality of life or aerobic fitness" (82), whereas a more recent systematic review and meta-analysis of studies of prehabilitation before major abdominal surgery found a reduction in overall and pulmonary morbidity with no difference in LOS (83).

Specific to NAC and AT change

We have considered above the evidence of a change in cardiorespiratory reserve following treatment with NAC, as well as the question of whether this might contribute to poorer surgical outcomes. Aside from the question of whether we should avoid NAC to mitigate this, there is a perhaps more pertinent question of whether any adverse effects can be overcome. In 2015, West *et al.* demonstrated a return to baseline fitness in their cohort of patients who

received neoadjuvant chemo-radiotherapy for rectal cancer by following a structured exercise-based prehabilitation programme, which certainly seems to suggest that the effects of NAC on fitness may be, at least somewhat, countered (84). To add balance to the argument, there have been studies in patients with oesophagogastric cancer, including a small study by Drummond et al in 2018 which demonstrated no significant change in AT post NAC as well as no evidence of a correlation between those who did experience a change in AT following NAC and outcome, therefore concluding that routine CPET testing is not indicated in this group (85). Given that CPET is a costly and time-consuming exercise, these findings should be considered, however what is clear is the need for large randomised controlled trials in this area.

There is the promise of a further influx of research to enhance our understanding in this area, including an international multicentre RCT led by a Dutch group concerning the colorectal population (86) as well as a UK study looking specifically at outcomes following prehabilitation in patients receiving NAC for OG surgery (87).

Optimisation of systemic effects and alterations to anaesthetic management

As always, the anaesthetic technique employed will depend on patient, surgical and anaesthetic factors – discussing all of these is beyond the scope of this article. A recently published review article discusses the impact of anaesthetic technique on cancer outcomes including the rationale for strategic application of anti-adrenergic, anti-inflammatory and anti-thrombotic therapies, to which the reader is directed (88). In this article we will tackle the anaesthetic adaptations, in a system-based approach, that can be employed to mitigate the risks of neo-adjuvant chemotherapy on the cancer patient during the peri-operative period.

A note on the timing of surgery—patients are likely to be presenting for urgent surgery, given the nature of the disease, but may present for unrelated surgery (which may be elective or emergency) (89). Therefore, there may be limited time for 'optimisation' compared with elective surgery, and this highlights the importance of the multidisciplinary approach to timing with respect to the balance of risks of surgery *vs.* disease. ERAS Society consensus guidance suggests optimal timing for oesophagectomy at 3 to 6 weeks following chemotherapy (90), and there is evidence from those receiving treatment for hepatic malignancy that a shorter duration of NAC along with a delay of a few weeks may confer a benefit in terms of morbidity and mortality (56).

Cardiovascular system

Pre-operatively, patients may present with cardiovascular symptoms, which may be due to pre-existing disease or have a causal or exacerbating relationship with treatment (89). Anthracycline-related heart failure has a better prognosis if detected and treated early (9,91). Acute toxicity relating to these drugs (including SVT and transient LV impairment) is rare (below 1%) and usually resolves upon cessation of treatment (9).

Pre-operative assessment provides an opportunity to identify pre-existing cardiovascular disease, as well as to guide the MDT discussion regarding the potential for further risk. Both oncologists and cardiologists will be involved in this management, and strategies (including dose modifications, and the use of less cardiotoxic agents) exist in order to modify cardiovascular risks (9). Evidence regarding medical treatment of heart failure is expanding in patients due to undergo chemotherapy, and decisions may be taken on an individual basis and include conventional treatment as well as treatment modification (9). In terms of coronary artery disease, the evidence of increased risk is largely from those receiving radiotherapy, though there may be an increased risk of coronary artery disease in those who receive chemotherapy in combination with radiotherapy (9,14). As such screening (and specialist involvement regarding treatment) for CAD might be warranted in patients at risk, as well as for those who develop symptoms during treatment (9,14). There is some evidence that exercise therapy may be beneficial in preventing or attenuating chemotherapy-induced cardiotoxicity (9).

Arrhythmia treatment may follow standard protocols especially in the immediate perioperative period, as well as identification and treatment of additional causative factors (such as contributing medication, electrolyte imbalances, acid-base disturbance etc. (14,92). Specialist input may be required following this, particularly regarding anticoagulation (9) or decisions regarding implantable electronic devices (92).

Formal guidance regarding the intraoperative management of patients at risk of cardiac toxicity following chemotherapy are lacking. It is likely that those undergoing major abdominal cases would have invasive

cardiac monitoring intra-operatively (though perhaps not specifically because of the cardiovascular risks related to NAC), just as those with significant cardiovascular disease might. It has been suggested in prior reviews that patients considered as being at higher risk of cardiovascular complications (based on history and examination as well as in the context of potential cardiotoxic therapy) should be monitored as such (intra-arterial blood pressure, cardiac output monitoring, 5-lead ECG), and that seems a sensible approach (22).

Respiratory system

There is little in the way of evidence regarding respiratory optimisation following chemotherapy-related pulmonary damage. A thorough history and examination should highlight acute factors that are modifiable (such as pleural effusion). There may be little to be done in the face of progressive pulmonary fibrosis, though an appreciation of its presence will guide anaesthetic management (ventilation strategies and post-operative destination). A low threshold for suspicion of respiratory tract infection, particularly in the immunocompromised patient will be important.

Guidance regarding management of patients who have been exposed to bleomycin has been offered informally, essentially recommending judicious use of oxygen (as low as possible with avoidance of hypoxia) (22).

Renal system

The nephrotoxicity associated with cisplatin use is due to acute tubular necrosis, and this is usually reversible (44), with requirement for renal replacement therapy unusual (43). There are case reports of enduring renal failure with the use of cisplatin (though these patients had additional risk factors for renal failure). Prevention would include close and frequent monitoring of fluid balance and renal biochemical markers, as well as adequate hydration (including up to 3 hours post-administration), to ensure adequate time for renal clearance of unbound platinum (whose level is correlated with nephrotoxicity) (22,44,93). Avoidance of nephrotoxic medications, including NSAIDs may be prudent in those at risk, as well as monitoring and management of electrolyte imbalance.

Nervous system

Many of the chemotherapy related neurotoxic effects are reversible upon cessation of administration (46,47). Although the perioperative significance is not clear, a low threshold for suspicion with respect to autonomic involvement (which may come from a thorough history) and subsequent additional intraoperative monitoring if required (IABP) may be sensible.

Of particular importance perioperatively would be careful neurological examination if regional anaesthesia were to be performed (for medicolegal reasons). Additionally, there is evidence that the peripheral neuropathy secondary to chemotherapeutic agents may be more susceptible to worsening with further insults (including local anaesthetic use), which may affect decisions regarding regional anaesthesia (46).

Hepatic system

In terms of perioperative management, the anaesthetist should have an awareness that there may be altered metabolism of medications including anaesthetic drugs (many NAC agents are CP450 inhibitors) (94). Impairment of clotting factor synthesis can result in coagulopathies which may restrict the use of regional techniques, as well as perioperative bleeding (25).

Much of the literature relates to identifying those at risk, and mitigating those risks, which requires an MDT approach which will likely include anaesthetists (51,55,56).

In terms of chemotherapy associated liver disease, identifying patient factors and therapies (including duration of treatment) that increase risk, monitoring during treatment, and timing of surgery to balance recovery from treatment effect with disease progression are probably most important (51,56,87). This remains an area of exciting ongoing research with emerging evidence to guide us.

Haematological system

The potential for bone marrow suppression should be considered prior to anaesthesia in patients receiving NAC therapy, as its sequalae carry several serious implications as outlined above.

Anaemia in cancer is multifactorial, and chemotherapy is one potential contributing factor. There have been extensive expert reviews written on this subject (95). The initial approach should be to identify the cause of anaemia and treat accordingly, and consensus guidance exists (96). Patient Blood Management programmes are in the ascendancy, encompassing pillars that guide management

through the entire perioperative period (97). Anaesthetists will be involved in most of these areas, beginning in pre-assessment clinic. Intraoperatively, adjuncts including tranexamic acid (98,99) and cell salvage (100) may play their role in reducing blood loss and transfusion, alongside identification and management of factors which may worsen a coagulopathy (including acidaemia and hypothermia). Point-of-care viscoelastic testing may help with early identification of coagulopathy and importantly prevent inappropriate use of blood products (101,102).

There should be a high index of suspicion for opportunistic infection, particularly in the neutropenic patient. Timing of chemotherapy prior to patient presentation for surgery is a key factor in judging the risk of neutropenia; with the highest risk being 7–14 days post chemotherapy and the risk reducing drastically if 6 weeks has passed since the last chemotherapy session (22). The life-threatening risk of opportunistic infection may outweigh the benefits of surgical intervention where patients are neutropenic, particularly when leukocyte counts are likely to rise within days to weeks. Where patients remain neutropenic for prolonged periods of time potentially delaying time critical surgery, discussion with haematologists and the role of Granulocyte Colony Stimulating Factors (G-CSF) should be considered. As always strict aseptic technique should be adhered to, particularly when invasive intravenous or arterial lines are placed, and local guidance for perioperative antibiotic prophylaxis should be followed. It may be prudent to closely monitor for infection in the perioperative period, including screening for sepsis using a validated screening tool.

With regard to the increased venous thromboembolism risk relating to NAC, a high index of suspicion should be maintained, as well as an appreciation that such patients may be receiving pharmacological prophylaxis preoperatively (particularly when considering timing of neuraxial blockade) (68).

Musculoskeletal and Gastro-Intestinal systems

A recent study demonstrated significantly less skeletal muscle mass index (SMI) reduction with enteral nutrition compared with parenteral nutrition during NAC, with an inference that there could be an associated impact on outcomes (including pulmonary) (69).

As discussed above, patients may experience nausea, vomiting, diarrhoea, and mucositis, and the anaesthetist should assess and treat hydration and electrolyte status perioperatively where required (22).

Pharmacological implications of NAC on anaesthetic agents

There is a growing evidence base indicating that the systemic effects of neo-adjuvant chemotherapy may alter the pharmacokinetic and pharmacodynamics properties of commonly used anaesthetic drugs. The mechanism underlying these changes are hypothesised to be largely due to the hepatic and renal effects of NAC therapy resulting in altered metabolism and excretion of anaesthetic agents. Central and peripheral nervous system sensitisation to anaesthetic agents post chemotherapy is another suggested mechanism (103-107).

Studies have shown that lower doses of propofol are required to elicit unconsciousness and maintain anaesthesia in patients that have undergone NAC treatment for breast cancer when compared to those that have not (103-105). Another study found that NAC resulted in a reduction in the minimum alveolar concentrations of sevoflurane required to block 50% of adrenergic responses to surgical stimuli in patients undergoing gastrectomy (106). Similar reductions in MAC values of sevoflurane and desflurane to maintain anaesthesia were seen in patients undergoing surgical treatment for hepatocellular carcinoma that had undergone NAC therapy (when compared to patients that had no preceding chemotherapy) (107). It has also been suggested that patients that have received NAC therapy may have a faster clearance of muscle relaxants and a quicker recovery of spontaneous respiration (105).

However, it is imperative to state that much of the literature surrounding this field is based on small sample-sized observational studies that are inherently venerable to bias with very limited generalisability. Furthermore, these studies in general found no changes in clinically orientated outcomes, e.g., hypotension, tachycardia, adverse effects, etc. between the NAC and control groups. As such, currently the implications of NAC on anaesthetic pharmacology are only of scientific interest until further research is carried out.

Conclusions

The use of chemotherapy prior to surgery is an exciting and rapidly evolving area. It has allowed advances in the surgical treatment of many forms of malignancy, including the transforming of previously unresectable disease to that which is amenable to resection. Alongside such advances

comes a duty to recognise and manage the undesirable effects of such treatments, and the anaesthetist can play a key role in the multidisciplinary team in this respect.

Many of the effects of chemotherapy may be relevant in the immediate perioperative period (cardiac, renal, hepatic), and we must maintain an awareness that patients may present for unrelated surgery outside specialist cancer treatment centres.

Comprehensive pre-assessment, a thorough multidisciplinary approach, appropriate monitoring and management (including anaesthetic management), along with shared decision making are key to achieving the best outcomes for our patients, and this is particularly true for this complex group.

There is a scarcity of high-level evidence regarding NAC from an optimisation point-of-view with regard to some organ systems, though this is increasing, and this is reflected in its increased presence in ERAS guidance (particularly with regard to timing of NAC and surgery at present). The results of studies concerning NAC and prehabilitation will add vital evidence to the literature.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://dx.doi.org/10.21037/dmr-21-29

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/dmr-21-29). CJ serves as an unpaid editorial Associate Editor-in-Chief of Digestive Medicine Research from Dec 2019 to Nov 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-21-29
Cite this article as: Barnes TC, Navaneetham S, Jones C. Neo-adjuvant chemotherapy and its anaesthetic implications for surgery—a narrative review. Dig Med Res 2021;4:55.