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Emergency surgery for patients with cancer receiving systemic anticancer therapy

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Introduction

Emergency surgery accounts for 750 000 hospital admissions in the UK, and nearly three million in the US annually[1]. Data from the National Emergency Laparotomy Audit (NELA) reveal 24 000 emergency laparotomy procedures are undertaken in England and Wales annually, with a growing incidence worldwide[2]. An estimated 19.3 million new cancers were diagnosed worldwide in 2020, with 4 million of those in Europe[3]. Of the 375 000 patients diagnosed with cancer each year in the UK, around 28 per cent will undergo systemic anticancer therapy (SACT) as part of their treatment[4]. Collectively, these statistics create a reasonable risk that any patient with cancer admitted for an emergency surgical procedure could be undergoing, or have recently undergone, SACT.

It is imperative that the emergency surgical presentation is taken in context of the oncological history including disease burden, treatment options, treatment response, and prognosis. This is in addition to the decision to operate in the emergency setting, which should be guided by the patient's physiology, our understanding of the natural history of the disease, and, most importantly, the patient's wishes. Risk *versus* benefit analysis may be challenging in this setting, even more so in patients who are actively receiving cancer treatment, and therefore multidisciplinary discussion is encouraged.

Chemotherapy agents cause a wide range of effects complicating the peri- and postoperative management of these patients. This paper aims to report the frequent side effects relevant to the acute perioperative setting of chemotherapy regimens used to treat the most prevalent cancers (summarized in *Tables S1 and S2*) and to assist surgeons to understand the risk profile of these drugs, as relevant to operating on patients with cancer who are currently receiving or have recently received SACT where a decision is made to proceed with emergency surgery.

Myelosuppression

Chemotherapy agents target cells with a high proliferative potential; thus, many patients experience adverse effects caused by the destruction of rapidly proliferating bone marrow progenitor cells. Myelosuppression refers to an overall downregulation in the production of blood cells, including red blood cells, white blood cells, and platelets. Chemotherapy induces apoptosis in multipotent progenitor and haematopoietic progenitor cells of the bone marrow[5]. The resulting complications include anaemia, neutropenia, and thrombocytopenia.

Anaemia

Anaemia identified preoperatively is known to be associated with increased morbidity and mortality following major surgery[6]. Anaemia can arise as a result of disease-related blood loss, chemotherapy and radiotherapy treatment, or other chronic comorbidities[7]. Anaemia is a common side effect of multiple chemotherapy agents as they suppress erythropoiesis. Carboplatin and cisplatin both inhibit erythropoiesis in the bone marrow and nephrogenic production of erythropoietin[8]. Anaemia should be correctly identified and, where possible, both red blood cell mass and erythropoiesis optimized before surgery. Despite transfusion being highly effective in reversing anaemia, intraoperative transfusions are proven to increase rates of infection, sepsis, and overall mortality[9]. In the emergency setting transfusion of packed red cells may be the only viable strategy to correct anaemia preoperatively. Iron and erythropoietin infusions, delivering high concentrations over short time periods, can also be administered perioperatively, to minimize the need for further transfusions, although the latter should be dosed with caution given that some data suggest an association with tumour progression[10,11]. The progression of anaemia postoperatively can also be prevented by minimizing surgical blood loss with an integrated approach requiring collaboration between surgical, anaesthetic, and haematology teams.

Thrombocytopenia

Thrombocytopenia can occur secondary to bone marrow toxicity from SACT. Carboplatin, an agent used commonly in the treatment of lung and ovarian cancer, is most associated with thrombocytopenia. Carboplatin suppresses megakaryocyte expression in the bone marrow, thereby reducing the production of platelets[12]. An increased risk of bleeding is an important consideration for both the operating surgeon and the anaesthetist, as even instrumenting the oropharynx during

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intubation may cause unwanted bleeding in an emergency. It is therefore necessary to liaise closely with a haematologist regarding perioperative platelet transfusion.

Neutropenia

Infection is the most frequent postoperative complication, with surgical site infection (SSI) constituting 31 per cent of all healthcare-associated infections[13]. The immunocompromised population are at higher risk of SSI and wound healing complications after surgery[14]. Neutropenia is a common side effect coinciding with the desired anticancer effects of many chemotherapy agents, occurring through suppression of the haematopoietic system[15]. Some chemotherapy regimens are associated with inducing more severe neutropenic complications such as febrile neutropenia. Docetaxel combined with cyclophosphamide is used to treat early-stage breast cancer, and febrile neutropenia is a complication reported in up to 69 per cent of patients[16].

Neutropenia renders patients vulnerable to infection, sepsis, and poor wound healing. Therefore, additional measures may be required to mitigate the risk of infection following emergency surgery. Prophylactic granulocyte colony-stimulating factor (G-CSF) can reduce the incidence and severity of febrile neutropenia and postoperative infections in high-risk patients[17]. Closed-incision negative pressure therapy is a technique shown to reduce the rates of SSI in emergency laparotomy and may therefore benefit neutropenic individuals at higher risk of infection[18]. Extended perioperative antibiotic prophylaxis may also be advantageous in mitigating the risk of postoperative infection[14]. In cases where prolonged periods of neutropenia have given rise to both bacterial and fungal infection, discussions with the treating oncologist and/or haematologist and the infectious disease team are necessary to ensure adequate antimicrobials are started.

Cardiotoxicity

Cardiovascular disease is a common cause of mortality in cancer survivors, attributed to the systemic inflammatory process of malignancy leading to ischaemic heart disease and congestive cardiac failure (CCF)[19]. Additionally, chemotherapy agents can cause a broad spectrum of cardiac dysfunction ranging from arrhythmias and hypertension to ischaemia and CCF[20]. Doxorubicin, an anthracycline indicated for the treatment of breast cancer, can cause early diastolic and late systolic dysfunction by inducing oxidative stress and cardiomyocyte apoptosis[21]. Targeted agents such as trastuzumab can induce cardiomyopathy in patients with breast cancer through a reduction in left ventricular systolic function[22]. Preoperative assessment is necessary to identify and manage any cardiac dysfunction that could be exacerbated by general anaesthesia and the surgical stress response. For patients with cardiotoxicity and cardiac failure, it is important to stabilize blood pressure, maintain fluid balance, and optimize end-organ perfusion and antiarrhythmic medications[23]. This requires close communication between the cardiology, anaesthetic, and surgical teams.

Renal impairment

Many chemotherapy agents are primarily excreted through the kidney, and certain agents can therefore damage the renal architecture. Chemotherapy-induced nephrotoxicity ranges from electrolyte imbalance and hypertension to acute interstitial necrosis and chronic kidney failure requiring dialysis[24]. Cyclophosphamide, an alkylating agent used to treat breast cancer, accumulates in the proximal tubules, causing dysfunction. The resulting complications include acute kidney injury, thrombotic microangiopathy, and electrolyte imbalances, including hyponatraemia and hypomagnesaemia[25]. Other nephrotoxic chemotherapy agents include cisplatin, gemcitabine, and methotrexate[26]. The volume status of the patient should be evaluated in the preoperative period and managed accordingly. Electrolyte and acid–base balances should be optimized prior to surgery and maintained in the intra- and postoperative phases, to minimize the risk of further nephrotoxicity. Altered renal function can implicate common postoperative management pathways such as dose adjustment to thromboprophylaxis, renally adjusted opioids if required for analgesia, and the avoidance of concomitant nephrotoxins such as non-steroidal anti-inflammatory drugs.

Side effects of immunotherapy

Checkpoint inhibitors such as nivolumab, pembrolizumab, and ipilimumab (commonly used for melanoma and lung cancer) have a broad range of immune-related adverse effects that can affect any organ, and include colitis, pneumonitis, nephritis, and endocrine organ dysfunction. Those of most relevance to an emergency surgical presentation include adrenalitis with adrenal axis suppression which may require emergency corticosteroid supplementation. Other endocrine axis dysfunction such as hyper- or hypothyroidism or hypopituitarism may also need specific emergency hormone replacement. If time allows, all patients on these agents should have a basic endocrine screen with a low threshold for corticosteroid replacement if profound hypotension, as well as involvement of endocrinology specialists to guide appropriate replacement in the perioperative period[27].

Embolism

Thromboembolism is a common complication of surgical procedures and a major cause of postoperative morbidity and mortality[28]. Patients undergoing SACT are at an increased risk of thromboembolism postoperatively, not only from the underlying malignancy inducing a hypercoagulable state[29], but also as thromboembolism is a common side effect of multiple chemotherapy agents. Specific biological and targeted anticancer agents, that inhibit angiogenesis via vascular endothelial growth factor pathways, including bevacizumab used in the treatment of colorectal and ovarian cancer, are particularly associated with venous and arterial thromboembolism[30]. As stated earlier, chemotherapy agents can frequently cause excessive bleeding and thrombocytopenia, and this risk must be taken in parallel when considering thromboprophylaxis, use of blood and blood products, and other drugs such as tranexamic acid.

Conclusion

A patient receiving SACT who requires emergency surgery represents a challenging scenario for any surgical team, and maintaining communication with the patient's treating cancer team is critical for case-by-case guidance. As demonstrated in this article, the effects of chemotherapy are broad but can be safely navigated in an emergency. We have provided a general overview to optimize pragmatically the adverse effects of chemotherapy in the perioperative setting, given time constraints

in the emergency surgical setting. There are several risk-mitigating management strategies that can be implemented depending on the toxicity encountered, including blood product transfusion, G-CSF, antimicrobial prophylaxis, cardiac assessment, and optimization of volume status. As with any complex clinical scenario, discussion with the patient and/or next of kin is vital, to ensure understanding of the risk–benefit profile when operating on high-risk patients with cancer. Finally, a clear understanding of the patient's anticipated prognosis should be gained in discussion with the patient's treating cancer clinician when making decisions regarding emergency surgery.

Author contribution

Kathryn Coulson (writing—original draft, writing—review and editing), Nigel Day (supervision, writing—review and editing), Madeleine Strach (supervision, writing—review and editing), and Paul Sutton (supervision, writing—review and editing).

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Supplementary material

Supplementary material is available at *BJS* online.

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