



Narrative review of blood management in the cancer patient undergoing surgery

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Abstract: Improvements in cancer screening programmes and diagnostics have meant that many cancers are now identified early in the disease process and therefore surgery can offer a potential cure. The incidence of cancer continues to increase worldwide and as does the need and capability for surgery. All surgery comes with a risk of blood loss and transfusion. Patient blood management (PBM) is now recognised as a multi-disciplinary team approach and has evolved over the last decade. Using a phased framework of pre-, intra- and post-operative pillars it aims to facilitate early identification and treatment of modifiable risk factors for peri-operative blood loss and thus reduce unnecessary blood transfusion. Anaemia is more prevalent in patients with underlying cancer, so the effects of significant peri-operative blood loss can be more profound and leads to increases in morbidity and mortality. Pre-operative anaemia is an independent risk factor for requiring a blood transfusion. Anaemia can arise from a number of causes; primary pathology, adjuvant chemotherapy and malnutrition are particularly prominent in a cancer setting. Pre-operative treatments include the use of blood, erythrocyte stimulating agent and intravenous iron therapy. Whilst allogenic blood transfusion might always remain a necessity where pre-operative anaemia is extreme or where there is catastrophic intra-operative blood loss, attention to early identification and intervention can modify blood usage. Intra-operative strategies for reducing transfusion in surgery may include advanced technologies such as cell salvage. Post-operatively adherence to transfusion threshold guidance can further reduce transfusion requirements.

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Introduction

Anaemia is common, estimated to affect 24.8% of the global population (1). Unfortunately, cancer rates continue to increase and in 2018 there were 18.1 million new cancer diagnoses with 9.6 million cancer deaths worldwide (2). Cancer is associated with higher rates of anaemia due to multiple factors with an estimated prevalence of greater than 40% (3). Anaemia is associated with worsening quality of life, as well as being an adverse prognostic factor (4).

Strategies to reduce unnecessary blood transfusions peri-operatively have led to the development of patient blood management (PBM), introduced by National Health System Blood and Transplant (NHSBT) in 2014. This is based on the three pillars of optimising a patient's own red cell mass, minimising blood loss intraoperatively and evaluating the tolerance of anaemia (5). We will explore how all elements of PBM can be utilised in patients with cancer undergoing surgery.

We present the following article in accordance with the

Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/dmr-20-61>).

Background

There is growing evidence that blood transfusions may have immunological effects that increase morbidity and mortality in patients with cancer (6). Keding *et al.* looked at how the introduction of a PBM system affected outcomes in patients undergoing abdominal oncological surgery (7). They showed a significant difference in 2-year overall survival after the introduction of PBM, 66.8% prior and 80.1% after ($P=0.001$) although no effect on short-term outcomes (7). Nevertheless, they demonstrated a 20% reduction in overall blood transfusions, had significantly more patients with normal haemoglobin levels prior to surgery, and where a patient was transfused, they received significantly less units per person after the PBM program was introduced (7). Interestingly they identified a single unit of blood as cut off threshold for impaired survival and quote a sensitivity of 75% and specificity of 61% associated with this (7).

Anaemia

The World Health Organisation defines anaemia as a haemoglobin less than 120 g/L in non-pregnant women over 15 years of age and 130 g/L in men (1). This cut-off may be outdated, and the current thinking is that 130 g/L should be used for all (8). Recent data looking at anaemia in cardiac patients showed an association towards an increased risk of death in those presenting for cardiac surgery with a haemoglobin less than 130 g/L (9).

The presence of cancer is associated with higher rates of anaemia, the cause of this is often multifactorial. The mechanisms contributing to the pre-operative anaemia are widespread; increased blood loss from the primary pathology, e.g., colon and other GI cancers, urinary system, gynaecological disease, as well as coagulopathy, surgical interventions, increased blood tests; bone marrow infiltration; chemotherapy and radiotherapy induced myelosuppression; chronic kidney disease; haemolysis, hemophagocytic syndromes; cachexia and malnutrition (10). Cancer pathophysiology itself can create immunoinflammation with increased hepcidin and blocking of iron absorption from the gut, which contributes to a functional iron-deficiency anaemia.

Treatment of peri-operative anaemia

Historically there were two options for the treatment of anaemia in cancer patients with the primary aim of symptom relief. The first involves transfusion of red cells which provides a rapid and usually predictable rise in haemoglobin and haematocrit levels. The second option is the use of erythropoiesis stimulating agents (ESAs). There are significant side effects and risks associated with both blood transfusions and ESAs. These include transfusion related reactions, cardiac overload, infections, and iron overload. Although strong evidence is still evolving, recent focus has promoted alternative pharmacological treatment of anaemia, in particular parenteral iron.

Red blood cell transfusions

Blood transfusions have been used for many years to reliably and predictably increase haemoglobin levels in symptomatic anaemia or during acute blood loss. Most studies to date have looked at patients undergoing surgery. Advances in technology have meant that through improved compatibility matching adverse reactions to blood transfusions are less common, but they can still occur and cause significant morbidity. One of the largest studies looking at outcomes after oncological surgery looked at 38,926 patients in the USA and showed that 16% of patients received blood transfusions (11). The receipt of a blood transfusion was associated with higher 30-day mortality, major complications, total number of complications and prolonged length of stay, independent of age (11).

Erythropoiesis stimulating agents

ESAs have been shown to reduce the amount of transfusions required in cancer patients and to increase quality of life (12). Approximately 10 years ago multiple studies showed that the use of ESAs in cancer patients conferred a significantly increased relative risk of mortality, particularly when they targeted haemoglobins >120 g/L, interestingly the effect was less pronounced in those receiving chemotherapy (13). This 'off label' usage of ESAs, targeting higher haemoglobin levels, was felt to be contributing to the increased mortality seen in these studies. Since then a large metanalysis confirmed that ESAs reduce the need for transfusion and can improve quality of life but at the expense of an increased risk of thromboembolic events and death (14). However, this metanalysis included studies which did not

follow the prescribed licensing doses. NICE currently only recommends ESAs for the treatment of anaemia in patients with cancer undergoing chemotherapy, their separate review only looked at studies which followed the licensing doses, and this showed no difference in the risk of death in those treated with ESAs (15). Current recommendations for ESA usage in the perioperative period are that they should not be used in patients undergoing elective surgery due to low rates of desirable effects and increased rates of potentially clinically significant thromboembolic events (16).

Iron deficiency anaemias & iron therapy

More recently there has been growing interest in treatment of iron deficiency anaemia pre-operatively. Iron deficiency (ID) defined as low transferrin saturations (TSAT <20%) reportedly affects 42% of patients with cancer (17). ID may be present with or without concurrent anaemia. ID is obviously a target for therapeutic intervention and should be considered in all patients with underlying malignancy whether they are due to undergo surgery or not, as it can be severely debilitating with significant effects on quality of life. Patients with pancreatic, colorectal, lung tumours, advanced disease or those undergoing chemotherapy appear to be most affected (10). Due to the inflammatory nature of the underlying pathology it can be more difficult to accurately assess iron status in patients with cancer.

Patients with or without cancer can develop two types of ID, absolute or functional. Absolute ID is a condition in which iron stores are depleted; contributing factors can be nutritional deficiencies or ongoing blood loss (10) and is defined as a ferritin <30 ng/mL in non-cancer patients. Functional ID is caused by the release of pro-inflammatory cytokines that cause hepcidin synthesis upregulation in the liver (9) with patients having normal or raised ferritin levels. Hepcidin is a key regulator of iron metabolism which acts by inhibiting ferroportin, the hepcidin receptor, thus preventing enterocytes from allowing iron into the hepatic portal system and thus reducing dietary iron absorption. Ferritin is an acute phase protein and is often raised in patients with cancer. It has been suggested that an altered cut-off <100 ng/mL be used as diagnostic criteria for absolute ID in patients with cancer (18).

Where time permits oral preparations of iron therapy may suffice. But in patients commonly with reduced absorption (from primary intestinal pathology, concurrent mucosal irritation from chemotherapy) or ongoing losses or functional ID, enteral absorption will not be effective.

Modern-day intravenous preparations have increased efficacy in treating this form of anaemia (19).

There is increasing evidence showing that the identification of anaemia and use of intravenous (IV) iron supplementation reduces red blood cell transfusions (20,21) and improves quality of life (21), in particular when used in conjunction with ESAs more than with oral preparations (22). There have been concerns for many years that the use of IV iron promotes an inflammatory response and can be associated with adverse cardiovascular events with current advice stating that it should not be given during an active infection. Currently there is mounting evidence that there is no increased risk of infection, cardiovascular events, or all-cause mortality but this remains an area of research (23).

Evidence regarding the effects of iron supplementation on tumour progression have as yet failed to show any effect; many studies have very limited observation periods and it is likely that with increasing use of iron we will begin to gather more evidence looking at this important area. There is an established link between iron overload, as seen in hereditary haemochromatosis, with the development of hepatic cancer (24) and high dietary intake of iron with colorectal cancer (25) but there is no clinical evidence to suggest supplementation leads to adverse oncological outcomes.

Current recommendations from the European Society of Medical Oncology about the use of iron and blood transfusions in patients with solid tumours or haematological malignancies have suggested ESAs be reserved for those patients with symptomatic anaemia undergoing chemotherapy (18). If patients have anaemia (Hb <110 g/L) and absolute ID (serum ferritin <100 ng/mL) they should receive iron treatment. If there is evidence of functional ID (TSAT <20% and serum ferritin >100 ng/mL) they should receive iron before treatment with an ESA. In cases of severe symptomatic anaemia (Hb <70–80 g/L) the administration of red blood cells should not be delayed (18). Many centres have now adopted similar guidelines in the pre-operative assessment clinic to identify pre-operative anaemia at the earliest opportunity and treat.

Pre-operative measures to assess and treat anaemia

The time to treat is often short when dealing with cancer as care pathways prioritise prompt surgery. This does

not mean that there is not time for pre-optimisation of haemoglobin stores. Often mild anaemia is one of the reasons for referral to specialist services for investigation of malignancy so identification and intervention can start as early as primary care. Therefore, from the point of initial General Practitioner referral, during interim investigations for potential malignancy, e.g., endoscopy, CT staging, to confirmed diagnosis, there are ample opportunities to assess baseline haemoglobin and iron stores. Where surgery is expedited parenteral preparations may be more efficacious; intravenous iron can start to elevate iron levels within a week, with changes in haemoglobin are seen at 2–3 weeks (26).

A thorough pre-operative history can highlight potential areas for optimisation. Concurrent usage of anticoagulants or antiplatelet agents can exacerbate ongoing blood loss and steps to risk stratify patients should be taken. Discussion with cardiologists, neurologists and haematologists may be necessary when planning peri-operative management of these medications.

Optimising physiological reserve through prehabilitation may have some benefits. Patients that can withstand lower haemoglobin levels may avoid the need for perioperative transfusions.

Formulating a patient specific plan prior to surgery is important. Firstly, ensuring that the patient has an adequate haemoglobin (>130 g/L) and that iron stores are replete. An estimate of predicted blood loss, considering the proposed surgery and any patient specific factors, should allow a plan for appropriate blood conservation strategies and appropriate transfusion triggers.

Intra-operative measures to minimise blood loss

The ideal time for scheduling patients for surgery should be a multidisciplinary decision. There may be situations where delaying surgery in order to optimise haemoglobin levels would benefit the patient to such extent that the associated risk of delaying surgery with potential cancer progression is outweighed. This obviously depends on the underlying malignancy and current disease state. Some cancers require neoadjuvant chemotherapy, and this has been shown to increase the incidence of anaemia to 90% (27). In these cases, it is paramount that steps are taken to optimise haemoglobin and iron stores prior to surgery.

During surgery there are both anaesthetic and surgical techniques that can be employed to minimise blood loss. Blood sparing surgical techniques such as minimally

invasive surgery and meticulous attention to haemostasis are essential. Pharmacological agents such as vitamin K or tranexamic acid can be used to further minimise blood loss but should be balanced against possible adverse events (28). Permissive hypotension has been used but there are associated concerns over end organ perfusion and long-term outcomes. Optimisation of cardiac output, ventilation, and oxygen in order to improve oxygen delivery to tissues should be employed in all cases. Patients should be kept normothermic and attention to acid-base balance is important in order to aid haemostasis. Anaesthetists should adhere to the restrictive transfusion thresholds which have been shown to be associated with reduced morbidity and mortality (5).

Cell salvage

Cell salvage was first introduced in 1974 and involves blood being suctioned from the surgical site. It is then filtered, centrifuged, and washed before being transfused back to the patient. Initially its use was contraindicated in cases in which the re-transfused blood was at high risk of contamination such as obstetric, colorectal and cancer surgery. In 1986 the American Medical Association Council on Scientific Affairs recommended against the use of blood salvage in cancer surgery (29). Since then evidence has shown cell salvage to be safe and effective in obstetric and colorectal surgery but attention should be given to minimising contamination from bowel contents or amniotic fluid (30). The use of cell salvage has remained controversial during oncological surgery due to concerns over seeding of the underlying cancer cells. Cell salvage has now been used extensively in urological cancer surgery and there is growing evidence that its use is not associated with disease recurrence and there is no increased morbidity or mortality (31). In contrast, the mounting evidence that allogenic blood transfusions are associated with increased rates of post-operative infections and disease recurrence should place greater emphasis on the use of cell salvage as a way of avoiding blood transfusions in this at-risk population (32). It has been shown in multiple studies that tumour cells are present in the scavenged blood, but they are also present in circulating blood before surgery (31). The process of surgical manipulation of tumours leads to an increase in cells disseminating into the circulation but that this does not correlate well with patient survival (31). The use of leucocyte depletion filters during cell salvage is currently recommended during cancer surgery; they have been shown to be highly effective at removing

contaminating tumour cells from salvaged blood (30,33).

Post-operative measures to minimise need for blood transfusions

Close attention to post-operative blood losses including minimising unnecessary blood tests are all important in maintaining appropriate haemoglobin levels. Dilutional anaemia is common in the post-operative setting and enhanced recovery measures should reduce this by resuming enteral intake as soon as possible after surgery thus minimising the need for intravenous fluids. Many patients undergoing major oncological surgery will be cared for in a high dependency or intensive care setting and this is associated with increased risks of stress ulcers which can lead to potential occult blood loss. Gastric protection strategies are employed in many enhanced recovery programmes and should be considered in all patients that are unable to resume enteral feeding immediately post-operatively. It is common in some institutions for all patients in a high dependency setting to receive ulcer prophylaxis. Ongoing attention to maintaining normothermia and acid-base balance is vital to ensure effective haemostasis.

Any hospital admission but particularly those involving surgery with prolonged immobility are associated with a significant risk of venous thromboembolism (VTE). If the patient has received a blood transfusion their risk of VTE is further increased and this is particularly evident in cancer patients (34). Anticoagulation and the use of thromboembolic stockings and or pneumatic calf compressors form the mainstay in minimising a patient's risk of VTE. Timing of anticoagulation postoperatively should be tailored to the patient and is usually led by the surgical team. Avoidance of secondary haemorrhage and prompt treatment of any underlying infections further minimise ongoing bleeding. Maintaining adequate haemoglobin levels postoperatively whilst adhering to the transfusion trigger targets is important in ensuring ongoing oxygen delivery to tissues at a cellular level. Adequate analgesia reduces the stress response to surgery and therefore minimises oxygen consumption.

Transfusion triggers

There has been a debate for many years about the use of liberal vs restrictive transfusion regimes and the effects on patient morbidity and mortality. Restrictive regimes vary in their thresholds but are generally 70 or 80 g/L compared

with liberal regimes with thresholds of 90 or 100 g/L. A large meta-analysis showed that restrictive transfusion strategies reduced the amount of red blood cell transfusions by 43% and were not associated with any increased morbidity or mortality when compared to the liberal regime (35). Unfortunately, they had insufficient data on many clinical subgroups including cancer patients.

Conclusions

Anaemia is common within the oncological population and can have a significant impact on a patient's quality of life and long-term morbidity and mortality. There is evidence that even a single unit transfusion can lead to impaired survival and thus all possible steps should be taken to avoid unnecessary transfusions. Patient Blood Management, involving a structured and thorough pre-operative assessment, identification of modifiable risk factors and the creation of a patient specific plan can optimise a patient own blood reserves, reduce blood loss and avoid transfusions if implemented early and effectively.

All oncological patients presenting for surgery should be managed using a multidisciplinary approach starting as early as possible, for example when a patient presents to primary care with initial symptoms in order to maximise the time for diagnosis and treatment of modifiable risk factors. Incorporating the current evidence base for patient blood management in the perioperative setting should ensure a greater proportion of patients present for surgery with optimal haemoglobin and iron stores. Adhering to the restrictive blood transfusion triggers should see lower transfusion rates perioperatively. This collaborative approach should lead to reduced morbidity and mortality in this increasingly complex patient population.

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