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Blood transfusion and patient blood management in cancer patients

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ABSTRACT

Anemia is common in cancer patients and linked to higher mortality, longer hospital stays, and reduced survival. Iron deficiency and the second most common form of anemia, anemia of chronic disease caused by elevated hepcidin levels, limit iron availability. Although red blood cell (RBC = transfusions quickly raise hemoglobin levels, they are associated with increased risks of tumor recurrence, infections, and reduced cancer-specific survival. Intravenous iron therapy and/or erythropoiesis-stimulating agents (ESAs) are effective alternatives to manage anemia. Patient Blood Management (PBM) offers a structured strategy to reduce transfusions by multiple approaches such as preoperative iron therapy, restrictive transfusion strategy and conserving blood during surgery. Clinical studies have shown that PBM significantly reduced transfusion rates, lowered infection risks, and shortened hospital stays without compromising safety. An individualized therapeutic approach seems beneficial in oncologic patients.

1. Introduction

Anemia is a prevalent and clinically relevant condition in cancer patients, linked to adverse outcomes such as increased mortality, treatment delays, and reduced quality of life. Despite well-established associations, uncertainties remain regarding optimal diagnostic and therapeutic approaches, particularly in the context of iron metabolism and transfusion-related risks. This review aims to provide a comprehensive overview of anemia pathophysiology in cancer, evaluates current treatment strategies, and critically assesses the role of Patient Blood Management (PBM) as a structured, evidence-based approach to improve patients' outcomes.

2. Anemia and its impact on cancer patients

Anemia is associated with increased in-hospital mortality, prolonged hospital stays, and a higher likelihood of admission to intensive care units [1]. This is particularly significant given the high prevalence of anemia, ranging from 25 % to 35 %, in patients admitted preoperatively to the hospital, which makes anemia diagnostics and therapy indispensable [2]. Over the past 10–15 years, this prevalence has remained largely unchanged, highlighting its continued relevance as a clinical issue [3,4].

In patients with solid tumors, prevalence of symptomatic anemia can reach up to 50 %. Under cancer therapy, it may increase up to 75 % [5]. Regardless of how it is assessed—whether through cross-sectional analysis or within specific patient cohorts—anemia

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represents a widespread issue affecting many patients. For instance, among patients undergoing esophagectomy for esophageal carcinoma, 64 % present with preoperative anemia, and 22 % received RBC transfusions preoperatively, while 68 % required transfusion postoperatively. In this patient population, anemia is associated with decreased overall survival, underscoring the need for effective treatment strategies [6].

3. Anemia and iron deficiency in cancer

Anemia is a common condition throughout the whole population and with additional triggers even with a higher prevalence among cancer patients. Due to the high prevalence of iron deficiency within the population, cancer can occur in patients with and without prior anemia [7]. Cancer leads to an induction of the iron regulatory hormone hepcidin, that is synthesized in the liver and leads to internalization and degradation of ferroportin, the sole iron exporter in humans [8]. Ferroportin is expressed in enterocytes, hepatocytes and macrophages. Induction of hepcidin and ferroportin degradation therefore inhibits iron absorption via enterocytes in the intestine, and via macrophages. The access to iron is therefore limited. Anemia of inflammation occurs, also named anemia of chronic disease – characterized by iron deficiency, hepcidin induction, and normocytic mild anemia [8,9]

A retrospective analysis of 598 patients with gastric cancer undergoing chemotherapy showed that an initial hemoglobin level of $\leq$8 g/dL was associated with reduced overall survival (OS) and progression-free survival (PFS) (*p = 0.009 and *p = 0.049, respectively). Furthermore, a hemoglobin drop of $\geq$3 g/dL had a significant impact on both, OS and PFS (*p = 0.039 and *p = 0.001, respectively). However, RBC transfusion, a common treatment for anemia in cancer patients, did not demonstrate a survival benefit [10] and should therefore be administered only after a thorough risk-benefit assessment. In addition, a meta-analysis of 9120 patients with gastric cancer and perioperative RBC transfusion revealed a higher cancer recessive rate [11].

Iron deficiency, iron deficiency anemia and the most common in cancer patients, anemia of inflammation are also prevalent in patients with solid tumors. The mechanism with an induction of hepcidin occurs like in non-solid tumor patients. Symptoms such as fatigue often negatively affect quality of life, which is a critical aspect for patients undergoing cancer therapy. A 2022 study of 186 patients demonstrated a significant improvement in quality of life—particularly in physical condition, emotional well-being, and fatigue—following intravenous (IV) iron administration [12].

4. Anemia treatment in cancer patients

Overall, the majority of cancer patients are treated with RBC transfusions, if they are anemic [13]. But alternatives exist and should be considered in each and every anemic patient according to the German transfusion guideline [14].

In the following sections, we will elucidate on the alternatives to RBC transfusion: oral iron therapy, intravenous iron therapy and erythropoietin.

The evidence supporting preoperative iron administration is strong, with multiple studies demonstrating its effectiveness to optimize hemoglobin levels, reducing the need for allogeneic blood transfusions, and improving overall patient outcomes [15]. In contrast, the evidence for intraoperative and postoperative iron supplementation remains limited and inconclusive. While some preliminary data suggest potential benefits, such as enhanced erythropoiesis and reduced postoperative anemia, robust clinical trials are still required to establish clear guidelines and confirm IV iron efficacy in these settings [16]. Further research is required to determine the optimal timing, dosing, and patient selection criteria for iron therapy beyond the preoperative phase [17,18].

4.1. Oral iron therapy

Oral iron therapy is the first-line therapy in iron deficiency anemia [19]. Therefore, oral iron supplementation remains a commonly used treatment for iron deficiency and iron deficiency anemia, particularly in outpatient settings. While it is generally well tolerated and associated with minimal adverse effects, its efficacy to restore hemoglobin levels and replenish iron stores is often limited [22]. Due to the mechanism of hepcidin induction, oral iron cannot be absorbed in cancer patients with inflammatory conditions, so that the hemoglobin level does not increase or the increase observed is often small. Interactions of oral iron therapy are mainly constipation, which is in case of opioid medication even more enhanced. Antibiotics may interact and absorbance rates might be decreased, if oral iron is taken. A side effect of magnesium improves congestion, but is off-label use. For oral iron supplementation, one tablet of iron on alternate days is currently recommended, as a daily medication may also lead to an induction of hepcidin [20].

Most patients with cancer report that oral iron does not improve hemoglobin levels, so that the mechanism of hepcidin induction and inhibition of iron absorption should be considered by laboratory markers of inflammation, transferrin saturation and ferritin measurement.

4.2. Intravenous iron therapy

In hospital settings, IV iron therapy is frequently indicated to correct iron deficiency more effectively. Especially in scenarios of cancer, the time point of administration has to be well considered. About 1 week after radiation or chemotherapy, the bone marrow function is impaired, and the anemia of inflammation has to match the indication defined as transferrin saturation below 20 % and ferritin below 300 ng/ml [21]. An intravenous iron infusion approach allows for a more rapid and significant normalization of hemoglobin levels and restoration of iron stores [22]. Responder show an increase of about 1 g/dl per week [23]. Various IV iron formulations are available, most of them exhibit high efficacy and safety [24]. Hypersensitivity reactions remain a primary risk in low

molecular weight compound, but high-molecular weight compounds show low anaphylactic rates.

A large meta-analysis from 2023 compared ferric derisomaltose and ferric carboxymaltose and found a significantly lower risk of hypersensitivity reactions with ferric derisomaltose (1.08 % vs. 0.14 %). Overall, both products demonstrated a very low risk of adverse reactions [25]. Additionally, IV iron administration has been shown to increase hemoglobin levels and reduce the need for RBC transfusions [26], suggesting that iron therapy alone may be sufficient in cases of iron deficiency anemia, potentially rendering RBC transfusions obsolete. Depending on the patient cohort, IV iron is economically advantageous. If the iron infusion prevents an RBC transfusion, the benefit is already obvious. The cohorts, who have been shown to benefit the most are gynecological and obstetric patients [27].

4.3. Erythropoietin therapy

Erythropoiesis-stimulating agents (ESAs) are sometimes used in cancer patients undergoing chemotherapy to manage anemia. Recent studies indicate that the combination of iron therapy (oral or IV) with erythropoietin yields a superior hemoglobin response compared to iron therapy alone [28,29]. In repetitive administrations, the hemoglobin levels should not exceed normal ranges, as those have been reported with higher cardiovascular complications in the guideline of 2014. A more recent meta-analysis from 2023 however indicated uncertain results [30].

5. Cell savage in cancer patients

In surgeries with a high risk of blood loss, intraoperative autologous blood transfusion (via autologous cell salvage) is a standard technique to minimize or eliminate the need for allogeneic blood transfusions.

A key scenario in oncologic surgery is the resection of the primary tumor in patients with non-metastatic disease.

In this scenario, cancer cells can be sucked with the blood into the blood collection container. The concerns regard the potential of a reinfusion of residual tumor cells and an increased risk of recurrence.

Circulating tumor cells (CTCs) are malignant cells that detach from the primary tumor and enter the bloodstream, either spontaneously or through autologous blood transfusion using intraoperative blood salvage techniques. While many CTCs could be eliminated due to mechanical stress from blood flow (shear stress) or immune surveillance by natural killer cells, a subset can evade destruction. CTCs employ various survival mechanisms, including platelet cloaking, which shields them from immune detection. Additionally, they can undergo epithelial-to-mesenchymal transition, enhancing their resistance to shear forces and immune-mediated clearance. The formation of CTC clusters further increases their survival and metastatic potential. Through extravasation, CTCs migrate into surrounding tissues, where they remain in a dormant state over month to years and induce macro metastases or further metastasis [31].

According to the Guideline of hemotherapy in Germany, there are two options to use the blood that might contain cancer cells: I) After radiation therapy, which is practically difficult in the operation room, as the autologous blood salvage cannot be disconnected from the cell salvage machine. II) Use of a leukocyte depletion filter (LDF) that withholds cancer cells. In a systematic review and meta-analysis the LDF was shown effective to deplete cancer cells in the range of 99.6–99.9 % [32,33].

In vitro studies have demonstrated that mechanical washing followed by leukocyte depletion effectively reduces *Epithelial cell adhesion molecule* (EpCAM)-expressing cancer cells and impairs their proliferative capacity, independent of irradiation [34].

The feasibility, efficacy, and safety profile of a newly developed CATUVAB procedure, which employs the bispecific trifunctional antibody Catumaxomab, were systematically evaluated in an *ex vivo* pilot study. This investigation aimed to assess the potential of the CATUVAB approach in effectively depleting residual EpCAM-positive tumor cells from autologous RBC obtained from cancer patients. These RBCs were generated using an innovative intraoperative blood salvage device, and the study sought to determine the clinical applicability of this method in ensuring a purer, tumor cell-free blood product for potential therapeutic use.

Tumor cells were identified in intraoperative blood samples from 10 of 16 patients, ranging from 69 to 2.6×10^5 cells. However, no residual malignant cells were detected in the final erythrocyte concentrates following the CATUVAB procedure. Pro-inflammatory cytokines IL-6 and IL-8, released during surgery, were reduced on average by 28-fold and 52-fold, respectively. Additionally, Catumaxomab was detected in 8 of 16 final EC products at significantly reduced and clinically uncritical residual levels, with a mean concentration of 37 ng [35].

Due to the highly promising results, a multicenter validation study on the removal of EpCAM-positive tumor cells during cancer surgery using the Catumaxomab/Catuvab device (*REMOVE* NCT06789224) was initiated (02/2022) and has already been completed (04/2024). The results are currently in the publication phase [36].

The REMOVE clinical study aimed to evaluate the safety and efficacy of the novel medical device CATUVAB in enabling the retransfusion of autologous erythrocyte products collected via an intraoperative blood salvage device during oncological surgeries with high blood loss. This single-group assignment study was conducted across six sites in Germany and enrolled a total of 136 patients. The primary objective was to demonstrate that the CATUVAB device, when integrated into autologous blood salvage procedures - including the use of LDFs - effectively eliminates EpCAM-positive tumor cells from intraoperative blood, ensuring a safer retransfusion process (ClinicalTrials.gov ID: NCT 06789224). [37].

This approach could serve as a step towards reducing the need for allogeneic blood transfusions in patients with EpCAM-expressing tumors and may pave the way for similar strategies in other tumor types.

In cancer surgery at a distant location of the cancer without metastases autologous blood salvage can be performed (e.g. hip surgery in a patient with breast cancer without metastases). In cancer patients with metastases the spread of cancer has already occurred, so

that autologous cell salvage can be used. In hematologic diseases, such as leukemia, or myelodysplastic syndrome, autologous cell salve can also be used, as these are hematologic diseases that are already present throughout the body's blood and there is no risk of spread.

6. Effects of RBC transfusions in cancer patients

A prospective observational study investigated the impact of RBC transfusion on fatigue and quality of life in patients with hematologic malignancies, who frequently experience debilitating fatigue. The findings confirmed fatigue levels comparable to those reported in other cancer populations and highlight the growing role of patient-centered outcomes in transfusion decision-making and clinical trials. Using three key measures - the 6-min walk test, FACIT-Fatigue score, and FACIT-Dyspnea score – the study demonstrated that RBC transfusion leads to clinically meaningful improvements in both functional capacity and fatigue [38,39].

These benefits, however, must be carefully balanced against potential risks, such as transfusion reactions or tumor recurrence.

A meta-analysis of 23 randomized controlled trials evaluated the impact of RBC transfusion on quality of life across various clinical settings, including postoperative patients following hip and cardiac surgery, individuals with hematologic malignancies, and other bleeding conditions. All included studies assessed changes in fatigue-related quality of life before and after transfusion under both restrictive and liberal transfusion strategies. None showed statistically significant impact for the liberal transfusion strategy concerning the endpoint [40].

Past studies have demonstrated a significant impact of perioperative RBC transfusions on tumor recurrence in gastric cancer [11], colon cancer [41] and bladder cancer [42]. A retrospective analysis from 1995 of 1051 patients undergoing curative resection for colorectal carcinoma, 42 % of whom received RBC transfusions, found no significant correlation between transfusion and recurrence. However, a significantly reduced cancer-specific survival rate was observed ($p < 0.0005$) [43].

More recent analyses have further clarified transfusion-associated risks. A 2016 retrospective study of 116 gastric cancer patients undergoing gastrectomy found that RBC transfusions were associated with a significantly increased risk of infections ($p = 0.002$ and $p < 0.001$), prolonged hospital stays ($p = 0.002$), and postoperative acute kidney injury ($p < 0.001$). Perioperative blood transfusion was also linked to reduced overall survival ($p = 0.078$) [44].

A 2022 meta-analysis of 19 studies included over 22,000 patients undergoing radical cystectomy for muscle-invasive bladder cancer found that perioperative RBC transfusion led to reduced recurrence-free survival ($p = 0.18$) and was significantly associated with decreased cancer-specific survival ($p = 0.008$) and overall survival ($p = 0.001$) [36].

Additionally, data from 792 patients over a 10-year period (2012–2022) showed a significant association between RBC transfusions and both, tumor recurrence and mortality, in patients undergoing nephrectomy and cystectomy [45].

These findings emphasize the importance of carefully weighing the necessity of blood transfusions and avoiding unnecessary transfusions whenever possible.

7. Patient blood management (PBM) in cancer surgery

Patient Blood Management is based on a multimodal approach to optimize blood management in medicine. Its primary goals are to reduce the need for blood transfusions, improve patient care, and minimize complications.

PBM is founded on three key pillars that form the basis of a patient-centered blood management strategy, to enhance patient safety and to ensure a more efficient use of resources.

The Three Pillars of PBM:

1. Optimization of Endogenous Red Blood Cell Production
   - Diagnosis, treatment and prevention of anemia, particularly in the preoperative setting
   - Supplementation with iron, vitamin B12, and folic acid in cases of deficiency
   - Use of erythropoiesis-stimulating agents
2. Minimization of Blood Loss and Optimization of Hemostasis
   - Reduction of blood loss through minimally invasive surgical techniques
   - Application of blood conservation strategies (cell salvage, hemodilution)
   - Coagulation management and avoidance of unnecessary blood sampling
3. Optimization of Physiological Tolerance to Anemia
   - Restrictive transfusion strategies with strict transfusion thresholds
   - Optimization of oxygen delivery (normovolemia, cardiopulmonary support)
   - Utilization of alternative therapeutic approaches (investigational oxygen carriers)

This structured approach enhances patient outcomes, reduces requirement on allogeneic blood transfusions, and promotes a more sustainable use of healthcare resources [46,47].

The WHO has already recognized the importance of PBM and urges member states to implement the corresponding strategies. (WHO-WHA63.12) [48].

Patient Blood Management was implemented in Germany at first in four University hospitals with more than 700.000 patients. The implementation of PBM with adherence to transfusion guidelines was safe for patients and showed in a non-superior analysis no increase in hypoxemia or deaths as well as similar levels of comorbidities. In contrast, renal failure occurred even less often [49].

Meanwhile, PBM was continued and implemented in more hospitals. A prospective follow-up study involved 1.2 million patients across 14 hospitals in Germany. We analyzed data before and after PBM implementation. Findings demonstrated a relative reduction in allogeneic blood transfusions by 13.9 % ($p < 0.001$, OR 0.86), with no inferiority in safety outcomes (5.6 % vs. 5.8 %) [4].

Beyond the reduction of RBC transfusions, PBM has been shown to cause lower infection rates, shorten hospital stays, and yield substantial economic benefits. A cost analysis following PBM implementation reported a societal cost reduction of over €2000 per patient in an example of elective gastrectomy, primarily due to these factors [50].

Although PBM is not specifically designed for cancer patients, its implementation in oncologic surgery has led to a significant reduction in RBC transfusions and lengths of in-hospital stay following colorectal cancer surgery, without increased complication rates [51]. Notably, the introduction of point-of-care (POC) diagnostics has significantly improved the appropriateness of RBC administration in the postoperative phase and should be used whenever possible [52].

8. Conclusion

Iron deficiency anemia and especially anemia of inflammation are common risk factors in cancer patients undergoing chemotherapy or tumor surgery. Left untreated, these conditions contribute to complications, prolonged stay in-hospital and increased mortality.

Although RBC transfusion effectively increases hemoglobin levels, it is associated with higher complication rates. Acute and preventive treatment strategies based on PBM—such as EPO and iron therapy (particularly IV iron for its superior efficacy) [53]—are safe alternatives with comparable benefits.

Intraoperative blood management still holds great potential, particularly in a safe use of autologous transfusion techniques in oncologic surgery.

CRediT authorship contribution statement

Simone Lindau: Writing – original draft. **Andrea U. Steinbicker:** Writing – review & editing.

Practice points

- Every patient undergoing high-risk tumor surgery should undergo a preoperative diagnosis for iron deficiency anemia or anemia of inflammation.
- Red blood cell transfusions should only be administered after a strict evaluation of the indication.
- Iron deficiency anemia should be treated with oral iron. Intravenous iron should be used in the setting of hospital treatment and in-hospital stay, if rapid correction of anemia is required, or if oral iron cannot work.
- Patient Blood Management should be implemented in all hospitals.

Research agenda

- Further randomized controlled trials are needed to investigate the safety of mechanical autotransfusion in tumor surgeries.
- Additional basic research is required to explore therapeutic or diagnostic approaches within the iron metabolism mechanism, alongside hepcidin.
- Studies that have recently been terminated will be published soon (REMOVE).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andrea U Steinbicker reports a relationship with Pharmacosmos and from HemoClear that includes: funding grants, each for an investigator-driven clinical trial. For experimental research regarding iron and bone homeostasis, and an epidemiological trial on anemia and hemochromatosis on fracture risk, AUS receives grants from the DFG (FerrOs-FOR 5146). The studies do not primarily focus on cancer patients. AUS has published articles on PBM implementation, and collaborated to meta-analyses about cell salvage use in cancer patients, as well as on the use of intravenous iron and cell salvage. In addition, the effect of intravenous iron or RBC transfusion has been investigated together with the implementation of PBM. AUS was the chair of the subcommittee of hemotherapy of the German Society of Anesthesiology and Intensive Care Medicine until 2021. There is no funding for the current review. S. Lindau declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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