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Red blood cell transfusion and its alternatives in oncologic surgery—A critical evaluation

Dania Fischer*, Holger Neb, Suma Choorapoikayil, Kai Zacharowski, Patrick Meybohm

Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Goethe-University Frankfurt/Main, Theodor-Stern-Kai 7, 60590, Frankfurt/Main, Germany

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ABSTRACT

Although blood transfusions have been used for more than 100 years and their potential to save lives is indisputable, there is still limited data on medium- and long-term outcomes after hemotherapy. Until recently, red blood cell transfusions represented the most commonly employed treatment for cancer anemia. As transfusions have been related to worse patient outcome in oncologic surgery, preventive strategies and alternative treatment approaches in the perioperative setting are warranted. This review aims to evaluate the evidence concerning the impact of transfusion on the course of malignant diseases with a focus on oncologic surgery and to provide a bundle of measures to improve patient care.

The perioperative period is pivotal in determining long-term cancer outcome. An increasingly recognized area for improvement during this highly sensitive period is the treatment of anemia for three main reasons: Firstly, anemia has been recognized as an independent predictor of poor prognosis in cancer patients. Secondly, anemia is largely undertreated. Thirdly and probably most importantly, anemia therapy relied and often still relies heavily on red blood cell (RBC) transfusions, which may be an often suboptimal stopgap treatment. Perioperative RBC transfusions should be kept to a minimum due to growing concerns regarding the associated risks, which this review tries to clarify by providing an update of recent literature. This review furthermore discusses treatments for anemia and provides best-practice approaches to improve perioperative management of *oncology* patients undergoing *surgery*.

1. Immunological effects of RBC transfusion

Until recently, blood transfusions have represented the most commonly employed treatment for cancer anemia (Ludwig et al., 2004). Whilst providing an immediate increase in hemoglobin, the benefits of transfusions are transient and concerns about their negative effects on patient outcome in the frame of oncologic surgery are rising. The main goal of cancer surgery is excising the primary tumour with tumour negative margins. During surgical resection, however, the load of circulating malignant cells may increase due to tumour manipulation and injury of tumour vessels (Miyazono et al., 2001). Transfusion-related immunomodulation (TRIM) is an important complex biological immune reaction culminating in immunosuppression, thereby potentially interfering with cancer development or progression (Cata et al., 2013). TRIM was formerly even used therapeutically to reduce renal allograft rejection before effective immunosuppressant drugs became available, underlining the extensive immunosuppressive potential (Opelz and Terasaki, 1978).

Well-established mechanisms for TRIM include interference with monocyte, cytotoxic and suppressor T-cell activity, release of immunosuppressive prostaglandins, and inhibition of interleukin-2 (IL-2) production (Cata et al., 2013; Vamvakas and Blajchman, 2007). Multiple cellular and humoral factors in blood products including residual leukocytes, apoptotic cells, cytokines, human leukocyte antigen peptides, extracellular vesicles, free haemoglobin and iron have been suggested to play a role in the pathogenesis of TRIM. In vitro studies show that the incubation of whole blood with supernatant of leukoreduced RBC units results in an increase in IL-6 and IL-10 and a decrease in lipopolysaccharide-induced release of Tumour Necrosis Factor-α production and in the induction of regulatory T-cell activation; the overall effect being strongly related to their length of storage (Karam et al., 2009). Despite pre-storage leukoreduction, which reduces leukocytes to less than 5×10^6/ unit, experimental studies have furthermore suggested that the remaining leukocytes in the RBC units mediate TRIM

* Corresponding author.
E-mail addresses: Dania.fischer@kgu.de (D. Fischer), Holger.neb@kgu.de (H. Neb), Suma.choorapoikayil@kgu.de (S. Choorapoikayil), Kai.zacharowski@kgu.de (K. Zacharowski), Patrick.meybohm@kgu.de (P. Meybohm).

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(Bordin et al., 1994).

Atzil and colleagues tried to identify whether red cells, leukocytes or soluble factors from RBC units display cancer promoting effects in two syngeneic murine tumour models of mammary adenocarcinoma and leukaemia (Atzil et al., 2008). They found that the transfusion of RBC units is an independent and significant risk factor for cancer progression in their murine tumour models. Herein, aged erythrocytes, rather than leukocytes or soluble factors, were accountable for the effects in a storage time- and cell volume-dependent manner. The effect was more pronounced in operated than in non-operated rats, furthermore underlining the significance of the surgical context. Mincheff et al. (1995) demonstrated a decreased recipient immune response following infusion of apoptotic cells from RBC units in a mouse transfusion model. The reason may be that apoptotic cells express phosphatidylserine on their surface, which in turn induces the secretion of anti-inflammatory cytokines such as IL-10 or TGF-β, and inhibit the secretion of inflammatory cytokines such as IL-12 or IL-1β, IL-6 and TNF-α (Saas et al., 2012). Next to apoptotic cells, RBCs also contain non-polar lipids, lyso-phosphatidylcholines and eicosanoids (Jacobi et al., 2000). The overall effects of these biological substances are immunosuppression and promotion of tumours (Soontrapa et al., 2011; Baratelli et al., 2010; Gately and Li, 2004). This is also the case for soluble HLA peptides (Magee and Sayegh, 1998). Cell-free haemoglobin, haem and iron from stored RBC units may also affect post transfusion immune function by inhibiting macrophage and THP-1 monocyte cell activation (Ozment et al., 2013). Additionally, it has been observed that the innate immune function (Natural Killer-cell activity) in the recipient—a key protective mechanism for local tumour control and against metastatic spread in the surgical patient – is strongly modulated even after autologous transfusion (Heiss et al., 1997). Effects of TRIM during the perioperative setting are illustrated in Fig. 1.

RBC units furthermore contain multiple extracellular vesicles, for example microparticles, which carry abundant bioactive molecules including different forms of nucleic acids and proteins that can markedly modulate cellular behaviour and eventually tumour microenvironment (Almizraq et al., 2016). Microparticles derived from stored RBC units, for instance, have been shown to induce the intrinsic pathway of coagulation and trigger tissue factor signalling (Horne et al., 2006; Fischer et al., 2017). RNA interference experiments suggest that tissue factor expression is an important effector of the K-ras-dependent tumourigenic and angiogenic phenotype in vivo (Yu et al., 2005). Hence, extracellular vesicles contained in blood products could potentially affect hallmarks of cancer such as thrombosis, immune evasion, angiogenesis, tumour invasion and metastasis as the involvement of the vascular system in malignancy encompasses not only angiogenesis but also systemic hypercoagulability.

2. Risk of transmitting or inducing cancer with transfusion

RBC transfusions might contain cancer cells or oncogenic viruses, potentially posing a risk to recipients. Usually, blood donors with a history of malignancy are permanently excluded from blood donation, but cancer is common enough to expect a certain proportion of blood donors to have undiagnosed cancer at the time of donation. As certain types of cancer emit malignant cells into the circulation at an early stage, RBC units may well contain malignant cells (Racila et al., 1998). RBC units may furthermore contain oncogenic viruses, for which the donor is not routinely tested. Examples are Kaposi's sarcoma-associated herpesvirus, Epstein-Barr virus, human papilloma virus and human T-cell lymphotropic virus 1, which could induce certain cancers in the transfusion recipient such as Kaposi sarcoma, T-cell leukaemia, hepatocellular carcinoma, nasopharyngeal carcinoma, cervical cancer and Burkitt's (Hladik et al., 2006; Chen et al., 2014; Martin and Gutkind, 2008).

The results of recent clinical studies trying to assess the risk of transmitting or inducing cancer with transfusion are conflicting. Yang et al. analysed a large cohort of UK women and found that those with a blood transfusion had a 2.63-fold risk for liver cancer and a 1.74-fold risk for non-Hodgkin lymphoma in the 5–9 years after their first known transfusion when compared to women without a history of transfusion (Yang et al., 2017). Patients with cancer or precancerous conditions before or at the time of transfusion were excluded. The increase in the prevalence is equivalent to about one additional liver cancer in every 2300 blood recipients and one additional non-Hodgkin lymphoma in every 1700 blood recipients. As the study was undertaken on a cohort transfused after the introduction of the nucleic acid amplification test for hepatitis C virus, this can be eliminated as a reason to explain the increased incidence of liver cancer. Cerhan et al. performed a case-control study in 759 patients diagnosed with non-Hodgkin lymphoma and found that transfusion was associated with a 26% higher risk of developing non-Hodgkin lymphoma (Cerhan et al., 2008). These findings are in contrast to a case-control study in 1591 confirmed cases of non-Hodgkin lymphoma, which did not find any association (Chow and Holly, 2002). However, these two studies stratified for different known risk factors, many risk factors are presumably unknown, and, yet again, blood transfusions might only have been a marker for underlying

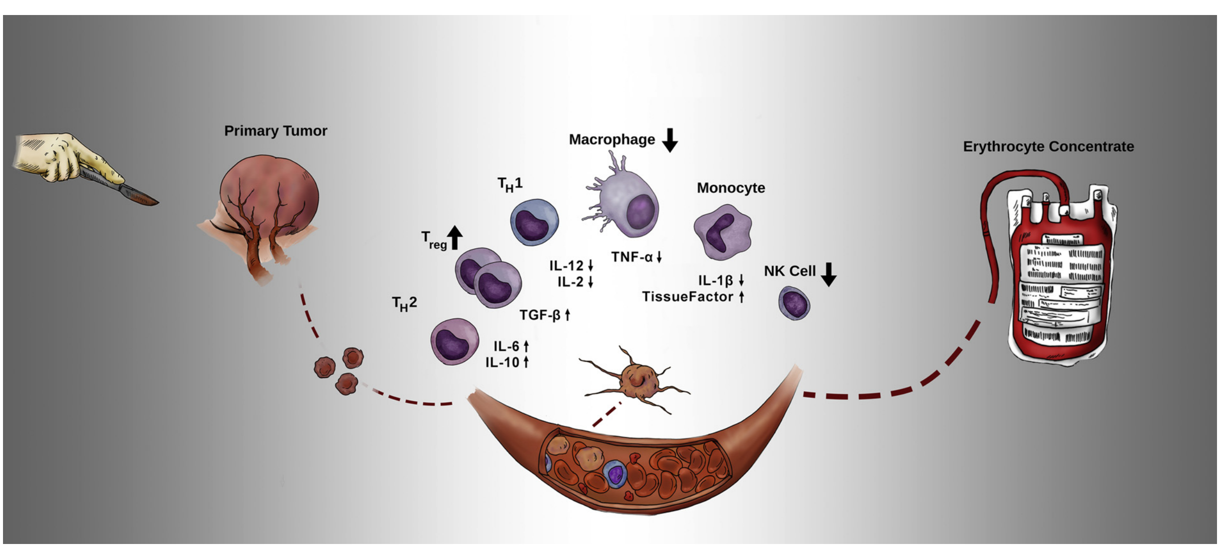

Fig. 1. Postulated Transfusion-related immunomodulation (TRIM) during surgery. Abbreviations: IL = interleukin, NK cell = natural killer cell; T_H1 = T helper cells Type 1; T_H2 = T helper cells Type 2; T_{reg} = regulatory T cells; TGF-β = transforming growth factor β; TNF-α = tumour necrosis factor α.

Table 1
Studies analysing the association between RBC transfusion and patient outcome after cancer surgery. Abbreviations: CI = confidence interval; HR = hazard ratio; n = number of patients analysed; OR = Odds ratio; RBC = red blood cell; vs = versus.

Study publication	Tumour type	Surgical procedure	n	Outcome
Acheson et al. (2012b)	Colorectal cancer	Colorectal cancer surgery	20,795	Cancer-related mortality: OR 1.71 (95 % CI 1.43–2.05, $p < 0.001$), combined recurrence-metastasis-death: OR 1.66 (95 % CI 1.41–1.97, $p < 0.001$)
Ejaz et al. (2015)	Pancreatic cancer (41.8 %), primary (23.1 %) or secondary (18.8 %) liver tumours	Hepato-pancreaticobiliary surgery	442	Overall survival after 1–2 RBC units: HR 1.76 (95 % CI 1.05–2.94, $p < 0.05$); after 3 + RBC units: HR 2.5 (95 % CI 1.35–4.63, $p < 0.05$), and risk-adjusted recurrence-free-survival (3 + RBC units: HR 2.91, 95 % CI 1.21–7.0, < 0.05)
Soubra et al. (2015)	Prostate (59.3 %), bladder (11.2 %), and kidney cancer (29.5 %)	Radical prostatectomy, radical cystectomy, or radical or partial nephrectomy	48,659	Radical prostatectomy: cancer-related mortality: HR 1.61 (95 % CI 1.24–2.10, $p < 0.001$) and overall mortality: HR 1.12 (95% CI 1.01–1.25, $p < 0.05$) Radical cystectomy: cancer-related mortality: HR 1.05 (95% CI 0.92–1.20, $p = 0.496$) or overall mortality: HR 1.10 (95% CI 1.0–1.2, $p = 0.055$) Radical or partial nephrectomy: cancer-related mortality: HR 1.37 (95% CI, 1.17–1.60, $p < 0.001$) and overall mortality: HR 1.40 (95 % CI 1.27–1.54, $p < 0.001$)
Sun et al. (2015)	Gastric cancer	Curative gastrectomy	9,120	Overall 5-year mortality: OR 2.17 (95% CI 1.72–2.74, $p < 0.001$) and 5-year cancer-related mortality: OR 2.57 (95 % CI 1.24–5.3, $p = 0.011$) and 5-year recurrence: OR 1.52 (95 % CI 1.08–2.15, $p = 0.017$)
Schiergens et al. (2015)	Colorectal liver metastases	Resection of colorectal liver metastases	292	Recurrence-free survival (32 vs. 72 months, $p < 0.01$), overall survival (48 vs. 63 months, $p = 0.08$)
Sutton et al. (2014)	Pancreatic adenocarcinoma	Pancreatico-duodenectomy	697	Median disease-free survival (13.8 vs. 18.3 months, $p = 0.02$) and overall survival (14.0 vs. 21.0 months, $p < 0.001$)
Mavros et al. (2015)	Pancreatic cancer	Pancreatic cancer surgery	3,646	5-year overall survival: OR 2.43 (95 % CI 1.90–3.10, $p < 0.05$)
Wang et al. (2014)	Lung cancer	Any form of resection	6474	Overall survival: HR 1.42 (95% CI 1.20–1.69, $p < 0.001$), recurrence rate: RR 1.33 (95% CI 1.11-1.61, $p < 0.01$)
Liu et al. (2013)	Hepatocellular carcinoma	Any form of resection	5635	5-year overall mortality: OR = 1.6 (95% CI 1.47–1.73, $p < 0.001$), tumour recurrence at one, three and five years: OR = 1.7 (95% CI 1.38–2.10, $p < 0.001$), OR = 1.22 (95% CI 1.08–1.38, $p < 0.001$), OR = 1.16 (95% CI 1.08-1.24, $p < 0.001$), respectively
Buchner et al. (2017)	Urothelial carcinoma of the bladder	Radical cystectomy	722	5-year-cancer-specific survival in patients with and without intraoperative RBC transfusion: 48 % vs. 67 % ($p < 0.001$)
Chipollini et al. (2017)	Urothelial carcinoma of the bladder	Radical Cystectomy	1,026	Recurrence-free survival, disease-specific survival, and overall survival (all $p > 0.05$)
Zaw et al. (2017)	Spinal metastases	Metastatic spine surgery	247	Overall survival: HR 1.15 (95 % CI 0.85–1.56, $p = 0.35$), progression-free survival: HR 0.87 (95 % CI 0.49–1.98, $p = 0.18$)

medical conditions and not causally related (Zhang et al., 2011). Another explanation could be that the prevalence of non-Hodgkin lymphoma risk factors differed in the two study populations, but both studies were undertaken in patients of the American west coast, albeit from different cities.

Another US population based case-control study in 552,951 elderly people identified from cancer registries and 100,000 matched controls found that transfusion received within the twelve months before cancer diagnosis was associated with significantly elevated risk of cancer (Riedl et al., 2013). However, the causation may be reverse as incipient cancers or cancer precursors cause anaemia.

A Scandinavian study conducted by Edgren et al. focused specifically on recipients of blood from donors who were later (up to five years after the donation) diagnosed with cancer (Edgren et al., 2007). Analysing data from 354 094 transfusion recipients after receiving blood transfusion from donors with subclinical cancer, no added risk of cancer was found within seven years (adjusted relative risk (RR) 1.00; 95% confidence interval (CI) 0.94–1.07). Median follow-up of the recipients included the seven years after transfusion. These findings did not suggest that blood transfusions from blood donors with subclinical cancer are associated with increased risk of cancer (as opposed to cancer cells transferred in an organ, bone marrow aspirate, or stem cell concentrate). In contrast, several case reports exist about haematogenous transmission of cancer during pregnancy from mother to foetus and after needlestick injury during surgery (Catlin et al., 1999; Baergen et al., 1997; Gartner et al., 1996). Additionally, there are reports on benign haematopoietic engraftment of donor cells, which survived and replicated in patients transfused after severe trauma for many years after transfusion, called microchimerism (Hirani et al., 2014; Lee et al., 1999). Although transfusion-associated microchimerism refers to the survival of donor leukocytes, the existence of microchimerism demonstrates that there are conditions of severe immune interference where donor cells are tolerated, even allowed to persist and to multiply in the transfusion recipient.

3. Long term outcome of transfusion recipients in oncologic surgery

In oncologic patients, blood transfusion is associated with poorer prognosis, but whether there is an independent effect of the transfusion is highly controversial. Most of the evidence stems from observational studies and when interpreting their results, one needs to keep in mind that there is a strong selection bias in the allocation of subjects to treatment and control arms (Isbister et al., 2011). Transfusion rates show significant inter-/intra-institutional and inter-/intra-operator variability, not necessarily related to patient comorbidity, severity of illness, complexity of surgery or cumulative blood loss, which may nevertheless also play a role difficult to account for in observational studies. Furthermore, the circumstances under which patients are given blood products in oncologic surgery are multifactorial and likely to influence different stages of tumour development, including initiation, promotion, malignant conversion, invasion, and metastasis.

A meta-analysis of 23 studies with 6474 surgically resected lung cancer patients showed that blood transfusion was significantly associated with earlier recurrence (Hazard Ratio (HR) 1.49, 95% CI 1.29–1.65, $p < 0.001$) and shorter overall survival (HR for the probability of death: 1.42, 95% CI 1.20–1.69, $p < 0.001$) (Wang et al., 2014). Another meta-analysis of 22 studies with a total of 5635 patients with hepatocellular carcinoma resection indicated that those who received blood transfusions had an increased risk of all-cause death at three and five years after surgery (respectively: Odds Ratio (OR) = 1.92, 95% CI 1.61–2.29, $p < 0.001$; OR = 1.60, 95% CI 1.47–1.73, $p < 0.001$) compared with those without blood transfusions (Liu et al., 2013). The risk of tumour recurrence was significantly higher at one, three and five years (respectively: OR = 1.70, 95% CI 1.38–2.10, $p < 0.001$; OR = 1.22, 95% CI 1.08–1.38, $p < 0.001$; OR = 1.16, 95% CI 1.08–1.24, $p < 0.001$). These studies focused on blood transfusions in the perioperative period, taking into account the transfusion of any blood product, i.e. RBCs, plasma or platelets. Potential confounders, such as disease stage, anaemia, and type of surgery, were reported and adjusted in only part of the included studies. Increased risk of mortality and tumour recurrence were also reported for patients with colorectal cancer (Horowitz et al., 2015; Acheson et al., 2012a; Amato and Pescatori, 2006). However, especially colorectal cancer resection is characterized by numerous processes that induce an abrupt elevation in the risk for the outbreak of pre-existing micrometastases and the seeding of new metastasis (Yamaguchi et al., 2000; Tohme et al., 2017). Again, most of the evidence is based on non-randomized studies with the major bias that patients with more advanced disease stages, severe surgical trauma or higher amount of blood loss might receive more transfusions. Examples of studies analysing a possible association between RBC transfusion and patient outcome are listed in Table 1.

4. Iron, erythropoietin and cell salvage to increase or preserve autologous red cell mass

Anaemia is very common in cancer patients and largely undertreated (Ludwig et al., 2004). Iron deficiency is one of the main causes and its supplementation is a therapeutic option recommended by several guidelines on the treatment of cancer patients with iron deficiency, either as monotherapy or combined with ESAs to enhance response (Park et al., 2015; Rizzo et al., 2010; Schrijvers et al., 2010). The overall goal of treatment in people with cancer-associated anaemia is to improve quality of life, to correct haemoglobin levels and to reduce transfusion requirements (Rizzo et al., 2010).

Generally, the efficacy of different strategies to treat anaemia with iron supplementation and/or ESA most likely depends on the form of iron deficiency as patients may have an isolated absolute or functional iron deficiency or a combination of both (Wilson et al., 2017; Ludwig et al., 2015). In patients with functional iron deficiency, oral iron is poorly absorbed in the duodenum. Further disadvantages of oral iron are that it requires a comparatively long treatment period and commonly causes gastrointestinal side effects, potentially limiting dosages and compliance. Nevertheless, Lidder et al. administered oral iron to patients ahead of colorectal surgery, which resulted in a significant rise in haemoglobin levels compared to the non-iron treated group (13.1 g/dl vs. 11.8 g/dl, 95% CI 0.26-0.97, p = 0.04) (Lidder et al., 2007). In this study, patients in the treatment group were less likely to require intraoperative blood transfusions (0 units vs. 2 units, p = 0.031, 95% CI 0.13–2.59). However, in a prospective study comparing oral versus intravenous iron, the latter was shown to be more effective (Keeler et al., 2017). The study included 116 anaemic patients undergoing colorectal cancer surgery, who were treated with either oral (ferrous sulphate) or intravenous iron (ferric carboxymaltose) in a short-term period before surgery. Increases in haemoglobin after treatment were higher with intravenous iron (median 1.55 (IQR 0.93–2.58) versus 0.50 (−0.13 to 1.33) g/dl, $p < 0.001$). However, there was no difference in blood transfusion rates between groups in this study (p = 0.47). In another prospective cohort study, Keeler et al. also showed that short-term treatment with intravenous iron ahead of surgery for colorectal cancer resulted in a rise in haemoglobin levels by 1.65 g/dl (IQR 0.5–2.3, $p < 0.001$), but they observed no reduction in the perioperative rates of blood transfusions (Keeler et al., 2014). Edwards et al, on the other hand, could neither observe significant increases in haemoglobin levels in 34 patients receiving intravenous iron at least two weeks before surgery for colorectal cancer compared to 26 receiving placebo nor differences in the rate of allogeneic blood transfusions (Edwards et al., 2009). The mean change in haemoglobin levels between recruitment and before surgery was −0.19 g/dl following iron therapy and −0.50 g/dl after placebo (p = 0.355). However, at recruitment, median haemoglobin levels for patients with anaemia were

11.8 g/dl in the iron subgroup and 12.4 g/dl in the placebo subgroup, so patients may not have been physiologically primed to utilize the parenteral iron.

Prospective studies on the effect of preoperative iron supplementation have mainly been undertaken in patients with colorectal cancer, where anaemia and likely ongoing blood loss are an integral part of the underlying pathology and surgery is an integral part of treatment. In other non-colon tumour entities, intravenous iron has been used for the prevention of anaemia regardless of iron status, for instance in patients with cervical carcinoma undergoing radiochemotherapy. In patients receiving 200 mg of iron sucrose intravenously, RBC transfusion rate was 40% compared to 64% in the control group ($p = 0.04$) (Kim et al., 2007).

Regarding potential short-term side effects of intravenous iron, it can be stated that modern preparations including low-molecular weight iron dextran, iron sucrose, and ferric gluconate are generally associated with few adverse events: Avni et al. (2015) systematically addressed safety concerns in a review and meta-analysis of 103 trials and found that, in 10,390 patients treated with intravenous iron, the rate of serious adverse events was statistically equal even when therapy was placebo-controlled in double-blind trials (RR 0.83; 95% CI 0.64–1.03, $I^2 = 41\%$). They found no increased risk of cardiovascular, respiratory, neurologic, thromboembolic, constitutional, or gastrointestinal severe adverse events with intravenous iron. They demonstrated that short-term adverse drug events such as hypersensitivity reactions or anaphylaxis were rare in low-molecular weight iron preparations, and, compared to oral iron, gastrointestinal adverse events were decreased and the risk of discontinuation of therapy was lower with intravenous iron.

In regards to patients with malignant diseases, not only short-term, but also potential long-term side effects have to be taken into account. Treatment with iron might favour neoplastic cell growth due to the high metabolic rate of tumour cells and the associated iron overturn. This could be especially important for cancer patients with functional iron deficiency – a cancer-induced immune response that might well protect against proliferation of tumour cells (Brookes et al., 2006; Weiss and Goodnough, 2005). In functional iron deficiency, iron is shifted from the circulation to the reticulo-endothelial system, making it less available for tumour cells. As iron is an essential micronutrient for cell development, growth and angiogenesis in both healthy and cancerous tissues, it is possible that iron deprivation in functional iron deficiency is an anti-cancer defense mechanism. It has been proposed to target iron metabolism therapeutically as iron depletion affects molecules involved in cell cycle control, angiogenesis and metastasis suppression including hypoxia-inducible factor-1 alpha, Vascular Endothelial Growth Factor 1, p21(CIP1/WAF1), cyclin D1 and the protein product of the N-myc downstream regulated gene-1 (Fischer-Fodor et al., 2015). In a human melanoma xenograft model, iron chelators showed broad antitumour activity and could even overcome resistance to established antitumour agents, although this effect might be primarily due to their effective redox activity, forming cytotoxic iron complexes intracellularly (Whitnall et al., 2006). Interestingly, in this experimental setting, the anti-proliferative effects observed were mostly tumour-specific, possibly due to the fact that cancer cells are more sensitive to iron deprivation because of their marked iron requirements.

However, many molecular mechanisms and functions of cancer-related functional iron deficiency remain unclear and the theoretical fears of stimulating tumour growth with a single iron supplementation might be outweighed by the postulated benefits of higher haemoglobin levels and lower RBC transfusion rates.

Iron has furthermore been shown to increase response to erythropoiesis-stimulating agents (ESAs). Gafter-Gvili et al., for example, undertook a systematic review and meta-analysis of trials mostly examining the addition of intravenous iron supplementation to ESAs for the treatment of chemotherapy-induced anaemia (Gafter-Gvili et al., 2013). They found that haematopoietic response was increased (RR 1.28, 95% CI 1.13–1.45), and the rate of blood transfusions both in trials with ESA (RR 0.76, 95% CI 0.61–0.95, seven trials) and without ESA (RR 0.52, 95% CI 0.34–0.80) was decreased. The reduction in blood transfusions was evident irrespective of the use of ESA. However, it has to be stated that the included studies were highly heterogeneous regarding the type of patients, malignancies, chemotherapy regimens, iron preparations, schedule, total dose of intravenous iron administered, different control groups (oral iron or no iron), and different types of ESA and schedule. Nevertheless, it can be concluded from this meta-analysis that the increase in haematopoietic response rate correlated with total iron dose, regardless of baseline iron status. Mhaskar et al. also evaluated the benefits and harms related to the use of iron as a supplement to ESA versus iron alone in the management of chemotherapy-induced anaemia (Mhaskar et al., 2016). They included eight randomized controlled trials, enrolling 2087 patients and found that the addition of iron to ESAs offers superior haematopoietic response, reduces the probability of RBC transfusions, and improves haemoglobin levels.

An additional potent option to treat anaemia is the use of ESAs, but these were associated with increased morbidity and mortality. A recent Cochrane review including 91 trials with 20,102 patients with cancer-associated anaemia found that RBC transfusions in recipients of ESAs were reduced (RR 0.65, 95% CI 0.62–0.68), but there was an increase in mortality (HR 1.17, 95% CI 1.06–1.29) (Tonia et al., 2012). Furthermore, the risk ratio for thromboembolic complications was increased (RR 1.52, 95% CI 1.34–1.74). A review of 51 randomised controlled trials examining the use of ESAs in the treatment of chemotherapy induced anaemia showed a relative increase of 57% in the risk of venous thromboembolism (95% CI 1.31–1.87) and a relative increase of 10% in the risk of mortality among participants (95% CI 1.01–1.2) (Bennett et al., 2008). However, these reviews analysed studies with enormous ranges in baseline epoietin alpha or beta dosage from 900 to 42,600 IU/week and differing treatment periods. Furthermore, some studies had haemoglobin targets up to 13 to 15 g/dl. It might be expected that short-term treatments with short-acting erythropoietin ahead of surgery cause less side effects than prolonged exposure to repeated bursts of high doses of EPO. This might also hold true regarding the potential for ESAs to affect disease progression in cancer patients. As erythropoietin may not only stimulate RBC growth and differentiation, but also exhibit anti-apoptotic effects on numerous cells and tissues as a pleiotropic growth factor. Various cancers were found to express receptors for erythropoietin on their surface, but it is unclear whether or not they show a clinically relevant growth response in vivo as there is conflicting evidence from clinical studies (Debeljak et al., 2014; Aapro et al., 2012). Henke et al, for instance, evaluated the effect of anaemia correction with epoetin beta on outcome of patients with head and neck cancer undergoing curative radiotherapy (Henke et al., 2003). ESA efficiently corrected anaemia among the patients, but locoregional progression-free survival was poorer with epoetin beta than with placebo (adjusted RR 1.62, 95% CI 1.22–2.14, $p < 0.001$). For locoregional progression, the relative risk was 1.69 (1.16–2.47, $p = 0.007$) and 1.39 (1.05–1.84, $p = 0.02$) for survival. However, a major bias of this study was a higher proportion of smokers and of patients with relapsed cancer allocated to the epoetin beta group. In a meta-analysis by Aapro et al., data from twelve randomized, controlled epoetin beta studies including data from 2297 patients showed a reduced risk for disease progression (HR = 0.85, 95% CI 0.72–1.01) when epoetin beta was used within its licensed indication (haemoglobin initiation ≤ 10 g/dl(-1)) (Aapro et al., 2009). Both the European (EMA) and US (FDA) regulatory authorities state that ESAs may be used to treat anaemia resulting from chemotherapy, and also to reduce the number of blood transfusions during and after certain major surgeries, but stress the possible side effects (Food and Drug Administration (FDA);German Medical Association). The European Society of Anaesthesiology (ESA) also suggests the preoperative treatment with ESAs if other causes of anaemia have been excluded or treated (Kozek-Langenecker et al., 2017). Risks of decreased survival and/or the increased risk of tumour progression or recurrence need to be evaluated carefully, discussed with the patients and adequate pharmacological thromboembolic prophylaxis provided.

In light of the possible side effects of RBCs, iron and ESAs, other measures in the prevention and treatment of anaemia should be exploited first. Meybohm et al. demonstrated in an epidemiological prospective observational study including about 130,000 patients that the implementation of patient blood management principles, including timely diagnosis and management of reversible anaemia as well as the use of blood-sparing techniques, can effectively result in decreased RBC transfusion rates and is safe for surgical patients (Meybohm et al., 2016, 2017). Gross et al. were able to demonstrate that the introduction of patient blood management in the treatment of cancer patients significantly reduced RBC usage even in a setting of restricted use of ESAs; there were no changes in mortality or length of hospital-stay (Gross et al., 2016). Keding et al. also showed that the introduction of a complex Patient Blood Management program focusing on anemia treatment before surgery, multimodal blood-sparing techniques, and a rationale transfusion regimen improve 2-year overall survival after oncologic surgery (Keding et al., 2018). Established strategies that can be applied to reduce unnecessary RBC transfusions is summarised in Table 2.

In oncologic surgery, the blood-sparing technique of autologous cell salvage is commonly not used out of fear to (re-)introduce malignant tumour cells into the blood stream. However, this precaution is increasingly challenged and, under certain circumstances, the use of intraoperative cell salvage may be safe to use in some forms of oncologic surgery. Stoffel et al, for instance analysed prostatectomies, during which wound blood from the tumour site was cell-salvaged and simply re-transfused to the patients without any further modifications. Cells expressing prostate-specific antigen (PSA) were used as a marker for tumour load; these were detectable in 88% of cell saver reservoirs after processing and centrifugation, but there was no difference in the number of cells expressing PSA in peripheral blood directly after surgery when comparing those patients that received cell-saver blood vs. those that did not ($p = 0.29$) (Stoffel et al., 2005). No PSA-expressing prostate cells were detected in any peripheral blood samples collected 3–5 weeks after surgery. Another study also found that the transfusion of autologous cell-saver blood, containing malignant cells, was not found to be an independent predictor of local recurrence or metastatic disease in prostate cancer (Davis et al., 2003). However, these were rather small studies and it could furthermore be possible that the PSA-producing cells identified in the cell-saver samples had sustained structural damage during cell-salvage processing that ultimately made them nonviable in an in-vivo environment as opposed to cells released into the vasculature due to surgical manipulation in the wound (Eschwege et al., 1995). Nevertheless, a meta-analysis of ten studies in patients with hepatocarcinoma, gastrointestinal cancer, cervical and prostate cancer suggests that outcome after the use of non-modified cell salvage is not inferior in terms of cancer recurrence to intraoperative allogeneic RBC transfusion (Waters et al., 2012). Overall, 769 patients included in this meta-analysis had received cell salvaged blood. Hence, cell salvage could be an additional means to reduce allogeneic blood transfusion in certain types of cancer, especially as the additional irradiation further reduces the risk of cancer cells included in the salvaged blood: by blood irradiation with 25–50 Gy at least a 12 log reduction of proliferating tumour cells can be achieved, so that the chance for a remaining tumour cell is less than 99.97% (Hansen et al., 1999; European Medicines Agency). A further option is the use of leucocyte depletion filters that allow the removal of tumour cells from blood salvaged during oncological surgery. A non-reinfusion study by Catling et al. analysed blood samples obtained at the operative field, after cell salvage and after filtration through leucocyte depletion filters, stemming from 50 patients undergoing major surgery for gynaecological cancers (Catling et al., 2008). They were able to show that no viable malignant cells were detected in any of the samples obtained after filtration through leucocyte depletion filters and only tumour fragments passed the filter, unable to cause metastasis. A study by Kim et al. involving patients who had liver transplantation as a result of hepatocellular carcinoma compared 121 patients who underwent intraoperative cell-salvage with the filtration through leucocyte depletion filters and 109 patients that received allogeneic blood transfusions (Kim et al., 2013). They found that use of intraoperative cell-salvage with leucocyte depletion filters decreased the rate of blood transfusions and had no effect on recurrence-free survival rates one, three and five years after surgery ($p = 0.314$).

5. RBC transfusion triggers

As there are only few prospective randomized controlled trials focusing on patients with malignancies, current recommendations are mainly based on non-cancer cohorts (Sim et al., 2015; de Almeida et al., 2015; Holst et al., 2014; Murphy et al., 2015; Villanueva et al., 2013; Docherty et al., 2016). The evidence from these studies supports a restrictive transfusion practice in several clinical settings, but it is generally recommended that the decision to transfuse should not be driven solely by the haemoglobin concentration, and no single criterion can be used as an indication for RBC transfusion. Only two prospective studies were carried out in critically ill oncologic patients, albeit from the same

Table 2
Strategies to optimise practices in routine care of patients undergoing cancer surgery.

Surgical and anaesthetic techniques
- Hypothermia should be avoided.
- Reduction of intraoperative blood losses:
  - Minimally invasive surgical procedures where possible
  - Use of haemostatic adjuncts
  - Cell salvage: Radiation of washed blood, filtration using leukocyte depletion filters.
- Intraoperative coagulation management.
- Empiric administration of tranexamic acid in certain procedures.
- Empiric therapy of platelet dysfunction (e.g. desmopressin).

Management of anaemia
- Management of reversible anaemia: Intravenous iron therapy should be started in patients with iron deficiency independent of the actual haemoglobin level.
- Treatment with ESAs may be considered in patients with haemoglobin levels < 12 g/dl (with an upper boundary of 12 g/dl) if other causes of anemia have been excluded or treated.
- Dosing suggestions: 1-3 subcutaneous injections of 600 IE/kg or 40,000 IE short-acting erythropoietin during the weeks ahead of surgery.

Allogeneic blood products
- Haemotherapy should be individualized and follow evidence-based guidelines in order to carefully balance the risks of allogeneic blood products against the risks of anaemia.
- A policy of single-unit transfusions should be adopted, where the need for transfusion is re-evaluated after every unit apart from cases of non-controlled surgical bleedings.
- Interdisciplinary blood conservation modalities such as restrictive phlebotomies should be applied.

working group with overlapping study periods, conducted as single centre studies and limited to the intensive care unit setting. In both studies, patients were randomized to a liberal (haemoglobin threshold, < 9 g/dl) or to a restrictive strategy (haemoglobin threshold, < 7 g/dl) of RBC transfusion during their stay on the intensive care unit (de Almeida et al., 2015; Bergamin et al., 2017). In the first study, conducted from January 2012 until July 2012, 198 oncological patients after various abdominal surgical procedures were included. Unfortunately, the regimen was not followed when patients left the intensive care unit. Indication to transfuse was - after release from the intensive care unit - up to the decision of the attending physician/s. The analysis of the transfusion triggers used on the wards indicates that the average haemoglobin concentration before transfusion was with 7.5 g/dl similar between groups. The authors report a lower 30-day and 60-day mortality in the liberal-strategy group (8.2% vs. 22.8%, p = 0.005; 11.3% vs. 23.8%, p = 0.022, respectively). There was a higher incidence of intraabdominal infection in the restrictive group than the liberal group (14.9% vs. 5.2%, p = 0.024), most likely explaining the most frequent causes of death at 30 days: septic shock and multisystem organ failure (24 patients). The observance of higher rates of infection in the restrictive group is in contrast to the results of a large meta-analysis, demonstrating higher rates of infections associated with (liberal) RBC transfusion (Rohde et al., 2014). Unfortunately, there is no information on intraoperative haemotherapy. In the other study conducted in the same hospital, 300 patients with solid cancer fulfilling the criteria of septic shock were randomized between June 2012 and May 2014 (Bergamin et al., 2017). At 90 days after randomization, mortality rates in the liberal group was lower than in the restrictive group (59% vs 70%, p = 0.03). However, transfusion strategy on the normal ward was again not part of the study and the statistical significance of this depends on 1 death and, again, these results stand in contrast to previous studies in septic shock (Holst et al., 2014). Hence, in order to better understand transfusion requirements of oncological patients, which may differ from other cohorts, larger multicentre randomized, prospective studies are required, and – most importantly - the transfusion trigger should be maintained at the same level for the whole hospital stay.

Generally, haemotherapy should be individualized and follow evidence-based guidelines in order to carefully balance the risks of allogeneic blood products against the risks of anaemia. A policy of single-unit transfusions should be adopted, where the need for transfusion is re-evaluated after every unit apart from cases of non-controlled surgical bleedings. To prevent iatrogenic anaemia, interdisciplinary blood conservation modalities such as restrictive phlebotomies should be applied (Fischer et al., 2014).

6. Conclusions

In the perioperative setting, multiple mechanisms might result in transmission, onset or progress of cancer. Structured patient blood management programs focusing on preoperative optimization of hemoglobin levels, blood-sparing techniques and standardization of transfusion practice were shown to improve patient outcome in oncologic surgery. Unfortunately, the mechanisms that led to the improved outcome remain unclear. We are currently left speculating and mechanistic studies are warranted to deepen our understanding especially of transfusion-tumor interaction on an immunologic level and its impact on cancer progression, being essential to counteract these potential effects. In the meantime, awareness of these issues is important in making individualized decisions on blood transfusion. Following patient blood management strategies, which include timely diagnosis and management of reversible anaemia, use of blood-sparing techniques and a tolerance of anaemia in haemodynamically stable patients should be applied. Transfusions should follow evidence-based guidelines, including “single-unit”-strategies in non-bleeding patients to prevent potential transfusion-related adverse events.

Conflict of interest statement

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Dania Fischer, MD, is practicing Anesthesia and Critical Care Medicine in Frankfurt since 2012 and gained work experience in transfusion medicine beforehand. She is a senior research assistant with a focus on transfusion associated immunomodulation and injury-induced immunosuppression in intensive care medicine. Dania Fischer received his MD from the University of Münster and is USMLE certified.

Holger Neb, MD, is practicing Anesthesia and Critical Care Medicine in Frankfurt a.M. at the Department of Anesthesia, Intensive Care Medicine and Pain Therapy at the University Hospital Frankfurt since 2010. He received his MD from the German University of Frankfurt a.M.

Dr. Suma Choorapoikayil, PhD, is a senior research assistant at the Department of Anesthesia, Intensive Care Medicine and Pain Therapy of the University Hospital Frankfurt. She studied Biology and obtained her PhD at the University of Cologne in 2008. During her time as a PostDoc at the Hubrecht Institute in the Netherlands and University of Montpellier in France she focused on the development of hematopoietic stem cells and tumor angiogenesis. In 2015, she joined the research group of Prof. Dr. Dr. Kai Zacharowski and Prof. Dr. Patrick Meybohm where she supports the program of Patient Blood Management.

Professor Kai Zacharowski, MD PhD ML FRCA holds the position of the Ordinarius and is the Director of the Department of Anesthesia, Intensive Care Medicine and Pain Therapy at the University Hospital Frankfurt since 2009. From 2006 until 2008 he was the Chair of Anesthesia and Intensive Care Medicine at the University Hospital Bristol. His research, teaching, and consulting interests are in both clinical and basic aspects of patient safety, transfusion and clotting, innate immunity, cardiovascular and critical care medicine. Professor Zacharowski received his MD from the German University of Mainz and his PhD from Queen Mary, University of London (where he was working with the Nobel laureate Prof. Sir John Vane → discovered how aspirin works). His scientific contributions are published in peer-reviewed journals such as Nature Medicine, Lancet, NEJM and Proceedings of the National Academy of Science and were awarded with numerous awards for Innovative Clinical Research. He is serving as Editor-in-Chief for the Journal of Anesthesia & Intensive Care Medicine as well as an Editorial Board member of numerous journals in Critical Care Medicine, Emergency Medicine and Anesthesia and is the CEO of the Lohfert Foundation. He is practicing Anesthesia and Critical Care Medicine in Frankfurt.

Professor Patrick Meybohm studied Medicine at the University of Göttingen including stays in the UK. He specialised in anaesthesiology, intensive care and emergency medicine at the University Hospital in Kiel before he came to Frankfurt/Main in 2012 where he currently is Deputy Director and Chair of the Clinical Research Unit at the Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy. He received a Master of Health Business Administration in 2014. His research activities have resulted in more than 250 publications, including more than 180 peer reviewed articles and 30 book chapters, and more than 7 Mio. Euro research funding (including German Research Foundation). He was granted numerous national and international awards. His research topics are Ischemic Remote-Preconditioning, Patient Blood Management, Perioperative Medicine, and Clinical trials in Anaesthesiology and Intensive Care Medicine.