Transfusion and Apheresis Science 56 (2017) 291–304

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Red blood cell transfusion in surgical cancer patients: Targets, risks, mechanistic understanding and further therapeutic opportunities

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ARTICLE INFO

Keywords:
Perioperative transfusion
Cancer recurrence
Red blood cell storage lesion
TRIM
Donor and recipient variation

ABSTRACT

Anemia is present in more than half of cancer patients and appears to be an independent prognostic factor of short- and long-term adverse outcomes. It increases in the advanced period of cancer and perioperatively, in patients with solid tumors who undergo surgery. As a result, allogeneic red blood cell (RBC) transfusion is an indispensable treatment in cancer. However, its safety remains controversial, based on several laboratory and clinical data reporting a linkage with increased risk for cancer recurrence, infection and cancer-related mortality. Immunological, inflammatory and thrombotic reactions mediated by the residual leukocytes and platelets, the stored RBCs *per se*, the biological response modifiers and the plasticizer of the unit may underlie infection and tumor-promoting effects. Although the causality between transfusion and infection has been established, the effects of transfusion on cancer recurrence remain confusing; this is mainly due to the extreme biological heterogeneity that characterizes RBC donations and cancer context. In fact, the functional interplay between donation-associated factors and recipient characteristics, including tumor biology *per se*, inflammation, infection, coagulation and immune activation state and competence may synergistically and individually define the clinical impact of each transfusion in any given cancer patient. Our understanding of how the potential risk is mediated is important to make RBC transfusion safer and to pave the way for novel, promising and highly personalized strategies for the treatment of anemia in surgical cancer patients.

Contents

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http://dx.doi.org/10.1016/j.transci.2017.05.015
1473-0502/

1. Red blood cell storage lesion

The bio-preservation of blood and blood labile products adds safety and adequacy to transfusion therapy by allowing its separation from blood donation in time and space. However, during cold storage in an artificial environment, red blood cells (RBCs) undergo time-dependent deterioration in several physiological aspects, collectively known as the "RBC storage lesion". In this context, functionally important disturbances in energy and redox metabolism, cell proteome, structure, geometry and removal signaling result in a distinct phenotype, which is associated with gradual RBC shape transformation to spherocytes, energy depletion and accumulation of free hemoglobin (Hb), lactate, potassium and extracellular vesicles (EVs) in the supernatant of the RBC concentrates, among other changes [1].

The susceptibility of donated RBCs to the adverse effects of storage varies significantly among eligible blood donors. Even the two "gold quality standards" of RBC unit, namely, in-bag hemolysis and 24-h *in vivo* recovery, exhibit large donor-dependent end-of-storage variability. Undefined donor-specific characteristics are strongly associated with day 42 hemolysis according to the results of a randomized, paired cross-over study [2]. Moreover, a large retrospective study of autologous RBC transfusion in healthy volunteers showed that end-of-storage RBCs had recoveries averaging around $82.4 \pm 6.7\%$, with some donors showing 24-h *in vivo* survival as low as 35–40% [3]. Several aspects of the RBC storage lesion, including cellular fragility, metabolic rate and accumulation of oxidative stress defects, are no longer considered incidental, but rather donor subject- or process-related changes, determined by genetic and other factors that modify the competence of RBCs [4,5].

Lack of uniformity between donations is further interwoven with the assessment of their post-transfusion performance and effects. The clinical impact of the RBC storage lesion is highly questioned, at least as a function of RBC "age". However, irreversible changes, like accumulation of free Hb, potassium and EVs in the supernatant seem to be related to compromised post-transfusion survival/efficacy and increased risk for adverse reactions in the recipients [6]. An increasingly "bioactive" supernatant containing cytokines, lipids and other biological response modifiers (BRMs) has the potential to modulate inflammatory and immunological responses in the recipient. Although the introduction of leukoreduction resulted in the restraint of cytokine accumulation, several BRMs remain in-bag and therefore, even leukoreduced RBC units can up-regulate inflammatory gene expression in circulating leukocytes (WBCs) [7]. Indeed, there is accumulative evidence *in vitro*, *ex vivo* and *in vivo* that the RBC units exert inflammatory and immunomodulative effects, and that transfusion can (and should) be regarded as an inflammation hit to the recipient [8]. Transfusion-related immune modulation (TRIM) includes both up-regulation of humoral immunity and down-regulation of cellular immunity and proinflammatory features [9,10] that may result in multi-organ dysfunction [11] or transfusion related acute lung injury (TRALI) in critically-ill recipients. Besides the "typical" BRMs, similar post-transfusion reactions can be mediated by EVs that represent "professional" mediators of intercellular communication. EVs shed by stored RBCs contain IgGs, expose PS and may reduce nitric oxide (NO) bioavailability, while those collected by older units are characterized by increased complement binding [12]. These EV features support a strong reactivity *in vivo* [13,14] that may underlie hemolytic reactions [15], TRALI and disturbance of the vasodilatory response [16].

However, the clinical impact of any RBC transfusion represents, in fact, the outcome of a functional interplay between recipient and donor variables and thus, it is equally dependent on recipient-related factors [4]. For example, following transfusion of G6PD-deficient RBCs, immediate hemolytic reactions have been reported in G6PD-deficient patients, neonates and recipients receiving oxidative medication [17] but not in other adult recipients post-tranfusion [18]. In addition, transfusion of old RBC units is associated with a pro-inflammatory cytokine response in preterm infants but not in healthy adult volunteers [19]. In this context, and owing to their high genetic and clinical heterogeneity [20], cancer patients are unique in terms of their treatment needs and disease specifics. Moreover, they represent one of the best available patient groups for studying blood transfusion recipient variation while moving forward to a more personalized transfusion medicine approach, which targets a "one to one" – "donor to recipient" matching.

This review aims to a gathering and critical reading of the laboratory and clinical evidence on the adverse, neutral or positive effects of RBC transfusion on surgical cancer patients, with emphasis on infection and recurrence. It further highlights the biological mechanisms that potentially mediate both of them, as a function of donation and recipient-associated parameters. From this synthetic view, new research targets and therapeutic opportunities may emerge.

2. The cancer patient as a specific recipient group

Transfusion of RBC concentrates aims to improve oxygen delivery to tissues in cases of anemia with inadequate physiological mechanisms of compensation. Anemia is present in almost 50% of cancer patients at some point during the course of the disease [21]. It is more frequent in hematologic malignancies, and increases up to 70% in the advanced period [22,23]. According to a recent large study, 63% of patients with advanced cancer were anemic, with 38% having moderate to severe anemia [24]. Anemia in cancer may be the result of treatment-related myelosuppression, occult bleeding, functional iron deficiency, erythropoietin deficiency due to renal disease and marrow involvement with tumor [25,26]. Patients with solid tumors who undergo surgery are at greater risk for development of anemia due to operative blood loss or hemodilution, particularly following complex and long-lasting surgeries. These patients may have anemia preoperatively, operatively, and postoperatively. It should be noted that major contributors to preoperative anemia are the anemia of chronic disease, nutritional deficiency, and chemotherapy, while tumor location and stage may influence the risk of preoperative anemia. Postoperatively, anemia can be worsened by adjuvant chemotherapy or radiotherapy [27].

It is therefore obvious that allogeneic blood transfusion is considered as an indispensable treatment in many cases, to treat signs or symptoms of anemia in the perioperative period. Furthermore, a cancer patient can also present with a defect in the primary and/or secondary hemostatic system, namely a decrease in platelet (PLTs) count or function and coagulation factors. Therefore, blood products such as PLT concentrates and fresh-frozen plasma are often administered to prevent bleeding and correct coagulopathy in those acutely bleeding. It has been estimated that 19.8% of the 15.7 million units of blood components transfused in the US during the year 2011 were for surgical patients [28] and that 15.1% of the RBC resources are allocated to oncology/hematology patients. Relevant data from Greece for the year 2013 showed that 29.3% and 14.6% of the RBC units were used in surgical and oncology/hematology patients, respectively [29].

In patients with cancer, anemia *per se* appears to be an independent prognostic factor of short- and long-term adverse outcomes. Nakamura et al. [30] demonstrated a significant inverse correlation between the preoperative Hb levels and C-reactive protein concentrations, suggesting a higher inflammatory status in anemic patients. Low Hb concentration may be associated with poor oncological outcomes in surgical patients, due to, *inter alia*, tumoral