CONTINUING EDUCATION

Transfusions of blood products and cancer outcomes

J.F. Velásquez, J.P. Cata

Department of Anaesthesiology and Perioperative Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA
Outcomes Research Consortium, Cleveland, OH, USA

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KEYWORDS
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Abstract
Approximately half of cancer patients scheduled for major surgery are anemic. Also, a significant number of patients will present to the operating room with low platelet counts and coagulopathic disorders. Unfortunately, administration of red blood cells, platelets concentrates and fresh-frozen plasma is associated with unwanted adverse effects including fever, hemolytic reactions and transfusion-related immunomodulation (TRIM). TRIM is a multifactorial immunologic phenomenon in the recipient mediated by donor leukocytes, microparticles such as ectosomes, and growth factors. As some of these molecules are secreted in a time-dependent manner, blood storage time may play an important in TRIM, although the evidence is limited. Perioperative administration of red blood cells and associated TRIM has also been associated with increased recurrence of certain solid tumors, such as colorectal, lung, and hepatobiliary tumors. In this continuing education article, we review the available evidence on how perioperative blood product transfusions can affect oncological outcomes, such as cancer recurrence.

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PALABRAS CLAVE
Cáncer; Recurrencia; Transfusiones sanguíneas

Resumen
Aproximadamente 50% de los pacientes oncológicos que se presentan para cirugía mayor están anémicos. Una buena parte de estos pacientes también presentan plaquetopenia y/o trastornos en sus vías de coagulación. Si bien la transfusión de productos derivados de la sangre se usan para corregir defectos perioropera tortios hematológicos, estos...
products han sido implicados como inductores de inmunosupresión. Esta última es de origen multifactorial ya que factores de crecimiento, leucocitos y macropartículas presentes en las bolsas de productos sanguíneos han sido implicado como algunos de los mecanismos de inmunosupresión. Es importante destacar que a la inmunosupresión asociada a las transfusiones perioratorias de sangre se la ha relacionado como uno de los mecanismos por los cuales existe una tasa de recurrencia de cáncer colorectal, pulmonar y hepatobiliar. En este manuscrito de formación continuada discutirá la evidencia existente acerca de la relación entre anemia, transmisión de productos de la sangre y recurrencia de cancer.

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Introduction

Anemia is present in almost 50% of the patients with cancer during the course of their disease. In this patient population, anemia can be the result of tumor or treatment related myelosuppression, occult bleeding or iron deficiency. Those patients with solid tumors who undergo surgery are at a higher risk of develop anemia in the perioperative period because of surgical-related bleeding or hemodilution. Therefore, perioperative infusions of packed red blood cells (pRBCs) are frequently used to treat sign or symptoms of anemia in the perioperative period. Patients with cancer can also present to surgery with a decrease in the count or function of their circulating platelets and/or coagulopathy. Therefore, the perioperative administration of blood products such as platelets concentrates (PC) and fresh-frozen plasma (FFP) is also a common practice.

Transfusions of blood products can be considered life-saving in some clinical scenarios; however, there are still a number of complications that can occur including viral or bacterial infections, hemolytic reactions, fluid overload, lung injury, hyperkalemia, and immune suppression. Transfusion-related immune (TRIM) modulation can be observed after the transfusion of pRBCs, PC and, perhaps a lesser extent FFP and is considered to contribute to the progression of minimal residual disease (MRD) to clinical metastasis particularly in patients who do not receive postoperative chemo-radiation as adjuvant therapy after surgery. TRIM is described as a consequence of the persistence of donor leukocytes on the host bloodstream, which may trigger a series of regulatory processes including the release in to the circulation of interleukin (IL)-10, suppression of IL-2 and natural killer cells (NK), leading to a predominant lymphocytic Th2 response (Fig. 1, Table 1). As a result, the ability of immune system to eliminate cancer cells is reduced. Also, the infusion of growth factors and pro-inflammatory cytokines have been suggested to exert a direct stimulatory effect on cancer cells and this be responsible of the growth of the postoperative MRD.

The goal of the review is to present some of the available evidence regarding the impact of perioperative anemia and blood product administration in the context of oncological surgery, in particular the possible association between blood product transfusions and cancer recurrence.

Development

Perioperative anemia and oncological outcomes

In patients with cancer, anemia per se appears to be an independent prognostic factor of short- and long-term complications. A recent study demonstrated that patients allocated to a restrictive (Hb < 7 g/dL) strategy of transfusion had worse prognosis than those who were transfused when Hb concentrations fall below 9 g/dL. This study indicates that in patients with cancer who undergo major cancer surgery the compensatory mechanisms to improve oxygen into different organs might fail below a threshold of 9 g/dL. Preoperative anemia is an independent risk factor for cancer recurrence; thus, it has been hypothesized that the association between blood transfusions and poor oncological outcomes may only represent the effect the

Figure 1 Potential mechanism of cancer recurrence after blood transfusions. The figure illustrates how the transfusion of blood products can lead to cancer cell proliferation and invasion by different mechanisms. TRIM: transfusion-related immune suppression. RBCs: red blood cells. Th: T helper response. T regs: T regulatory cells. NK: natural killer cells.
Transfusions of blood products and cancer outcomes

Table 1  Effects of blood transfusion on cellular and soluble mediators of the immune system.

<table>
<thead>
<tr>
<th>Outcome(s)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK cell activity</td>
<td>Significant and prolonged reduction in NK cell activity in patients transfused with nonleukoreduced RBCs</td>
</tr>
<tr>
<td>Long-term kinetics of donor leukocytes in recipients' circulation</td>
<td>0.5–10% of circulating leukocytes in recipients were from donor (microchimerism)</td>
</tr>
<tr>
<td>Neutrophil activity</td>
<td>Strong inhibition of chemokinesis after transfusion; only supernatant of nonleukoreduced RBCs impaired chemotaxis of neutrophils</td>
</tr>
<tr>
<td>Circulating concentrations of IL-6, IL-10, IL-12, and procalcitonin</td>
<td>Concentrations of IL-6 were significantly higher only after transfusion of &gt;4 units of nonleukoreduced blood compared to leukoreduced blood; no differences in circulating concentrations of other cytokines</td>
</tr>
<tr>
<td>Circulating pro- and anti-inflammatory cytokines; neutrophil activation</td>
<td>No significant impact of transfusion of leukoreduced blood on circulating concentration of IL-6, IL-2, IL-4, IL-5, IL-10, IL-12-p70, IFN-γ, or TNF-α or on neutrophil activity</td>
</tr>
<tr>
<td>Effect of storage on complement activation</td>
<td>Time-dependent increase in concentration of complement C5b9</td>
</tr>
</tbody>
</table>

IL, interleukin; IFN, interferon; RBC, red blood cells; RCT, randomized controlled trial; TNF, tumor necrosis factor.

intervention (blood transfusion) to correct low hemoglobin concentrations.7–9

In the context of surgery, low hemoglobin concentrations may be associated with poor oncological outcomes due to several reasons including: (1) tumoral hypoxia which can trigger adaptive mechanisms that may alter the phenotype of the cancer cells turning them more aggressive and (2) the release of pro-inflammatory cytokines that can stimulate tumor growth.10 Moreover, a recent study indicates that there is significant inverse correlation between the preoperative concentrations of Hb and C-reactive protein suggesting that anemic patients have a higher inflammatory status.11 Based on these premises, correction of anemia before surgery could be indicated to improve clinical outcomes in patients with cancer; however, the combination of anemia and blood transfusions is more deleterious that each of them individual.12

Transfusions of red blood cells

For a long time it has been recognized that perioperative blood transfusions can have a negative impact on cancer-related survival (Table 2). The type (allogeneic versus autologous) and volume of pRBCs transfused, the timing of the transfusion, the leukoreduced status of the blood units, and the age of the RBCs at the moment of transfusion are all factors that have been implicated in TRIM.3 Therefore, a large number of studies have been conducted with the goal of evaluating the impact of those factors on cancer outcome and cancer related survival. Most studies indicate that the perioperative use of leukoreduced or "newer" blood units does not improve cancer-related survival.13–16 The effect of the administration of allogeneic, in comparison to autologous, blood transfusions on cancer recurrence is still debatable and it appears to be tumor specific. For instance, allogeneic blood transfusion was an independent risk factor for recurrence after head and neck surgery but not in patients with rectal and prostate cancer.17–19 According to the current evidence, the use of acute normovolemic hemodilution and blood recovered (cell-salvage) from the operative field are accepted and safe techniques to reduce the use of blood transfusion in the perioperative period of cancer surgery and they have not been linked to an increase in cancer recurrence.20

The results of two recent meta-analyses indicate that pre-, intra-, and postoperative blood transfusions (compared to no blood transfusion) are an independent risk factor for colorectal cancer recurrence.21,22 Similar results have been shown in patients who underwent hepatobiliary and pancreatic carcinoma. Thus, Yao et al. found that allogeneic blood transfusions were an independent risk factor of poor oncological outcomes in patients with ampullary cancer of the pancreas and Kneuertz et al. demonstrated that the risk of recurrence increased 10% per unit of blood transfused in patients with pancreatic carcinoma.23,24 In line with this evidence, two different meta-analyses that included patients with lung cancer showed that perioperative blood transfusions were associated with a 25% and 42% increase in mortality and cancer recurrence when all cancer stages are considered and a 55% higher risk of recurrence in subjects with stage I.25,26 Similar results were found in studies that investigated the effect of the administration of RBCs in patients with head and neck cancer and a reported a strong association between perioperative blood transfusion and risk of recurrence.27 In patients with esophageal cancer, perioperative transfusion of packed RBCs was associated with a 60% reduction in survival rate.28

It is worth noticing that the association between perioperative blood transfusion and cancer recurrence has not been demonstrated in patients with prostate cancer. Two recent studies conducted by Yeoh et al. and Boehm et al. reported that patients who received a transfusion perioperatively did not have a higher risk of biochemical cancer recurrence, systemic progression, prostate cancer-related death, or all-cause death than patients who did not.29,30 In patients with renal cell and urothelial carcinomas, the literature has shown conflicting results; nonetheless, most studies demonstrate a significantly shorter overall survival in transfused patients.31–34 Blood transfusions are frequently administered to women who undergo debulking surgery for ovarian cancers. Although, tumor stage and the quality of postoperative cytoreduction appear to be more important predictors of mortality and cancer recurrence than blood transfusion, De Oliveira et al. found that the perioperative administration of RBCs was associated with an increased
Table 2  Studies addressing the association between perioperative blood transfusion and recurrence-free or cancer specific survival.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer</th>
<th>Type of study</th>
<th>Total no. of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acheson et al. (2012)</td>
<td>Colorectal</td>
<td>Meta-analysis</td>
<td>20,795</td>
<td>Blood transfusion was associated with an increased risk of cancer-related mortality (OR, 1.71, 1.43–2.05) and recurrence-metastasis-death (OR, 1.66, 1.41–1.97)</td>
</tr>
<tr>
<td>Yao et al. (2008)</td>
<td>Ampullary</td>
<td>Meta-analysis</td>
<td></td>
<td>Transfusion was associated with reduced survival (RR, 2.55, 1.59–4.1)</td>
</tr>
<tr>
<td>Luan et al. (2014)</td>
<td>Lung</td>
<td>Meta-analysis</td>
<td>5915</td>
<td>Patients who received a transfusion had shorter disease-free survival than patients who did not (RR, 1.42, 1.20–1.67)</td>
</tr>
<tr>
<td>Wang et al. (2014)</td>
<td>Lung</td>
<td>Meta-analysis</td>
<td>6474</td>
<td>Transfusion was an independent risk factor for poor DFS (HR, 1.49, 1.29–1.65) and was associated with a higher risk of recurrence (RR, 1.33, 1.11–1.61); in patients with stage 1 disease, transfusion was associated with decreased DFS (HR, 1.7, 1.20–2.42) and a higher risk of recurrence (RR, 1.55, 1.20–1.99)</td>
</tr>
<tr>
<td>Woolley et al. (1992)</td>
<td>Head and neck</td>
<td>Meta-analysis</td>
<td></td>
<td>Transfusion was associated with a higher risk of recurrence (OR, 2.6, 1.9–3.7)</td>
</tr>
<tr>
<td>Linder et al. (2013)</td>
<td>Renal cell</td>
<td>Retrospective</td>
<td>2318</td>
<td>Overall mortality (HR, 1.23, 1.04–1.23) but not cancer-specific mortality (HR, 1.15, 0.87–1.53) was associated with transfusion of pRBCs</td>
</tr>
<tr>
<td>Kluth et al. (2014)</td>
<td>Bladder</td>
<td>Retrospective</td>
<td>2895</td>
<td>RFS and CSS of patients who received a transfusion were similar to those of patients who did not</td>
</tr>
<tr>
<td>Morgan et al. (2013)</td>
<td>Bladder</td>
<td>Retrospective</td>
<td>777</td>
<td>For every 2 units of pRBCs transfused, the risk of death increased by 17% (HR, 1.17, 1.01–1.36)</td>
</tr>
<tr>
<td>Linder et al. (2013)</td>
<td>Bladder</td>
<td>Retrospective</td>
<td>2060</td>
<td>Patients who received a transfusion had a higher risk of recurrence (HR, 1.20, 1.01–1.42) and death (HR, 1.31, 1.10–1.57) than patients who did not</td>
</tr>
<tr>
<td>De Oliveira et al. (2012)</td>
<td>Ovarian</td>
<td>Retrospective</td>
<td>136</td>
<td>Each unit of pRBCs transfused increased the risk of recurrence by 62% (RR, 1.62, 1.04–21.54)</td>
</tr>
<tr>
<td>Morgenstern et al. (2012)</td>
<td>Ovarian</td>
<td>Retrospective</td>
<td>333</td>
<td>Patients who received a transfusion had higher RFS (HR, 1.37, 0.76–2.47; not statistically significant) than patients who did not</td>
</tr>
<tr>
<td>Yeoh et al. (2014)</td>
<td>Prostate</td>
<td>Retrospective</td>
<td>1137</td>
<td>Transfusion was not an independent risk factor for systemic progression (OR, 0.88, 0.39–1.99) or cancer-related survival (OR, 1.69, 0.44–0.48)</td>
</tr>
<tr>
<td>Chalfin et al. (2014)</td>
<td>Prostate</td>
<td>Retrospective</td>
<td>7443</td>
<td>No association was found between type of blood (HR for allogeneic versus no transfusion, 1.02, 0.73–1.43; HR for autologous versus no transfusion, 1.02, 0.88–1.18) or CSS (HR for allogeneic versus no transfusion, 1.55, 0.62–1.09; HR for autologous versus no transfusion, 0.82, 0.62–1.09) and cancer recurrence</td>
</tr>
<tr>
<td>Ford et al. (2008)</td>
<td>Prostate</td>
<td>Retrospective</td>
<td>611</td>
<td>Neither autologous (HR, 0.72, 0.39–1.33) nor allogeneic (HR, 1.04, 0.486, 2.253) pRBC transfusion was associated with poor survival after surgery</td>
</tr>
</tbody>
</table>

CSS, cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; pRBCs, packed red blood cells; RFS, recurrence-free survival; RR, relative risk.

* Ranges are 95% confidence intervals.
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<table>
<thead>
<tr>
<th>Cancer</th>
<th>Risk of recurrence</th>
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<tbody>
<tr>
<td>Colorectal</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>Head and Neck</td>
<td></td>
</tr>
<tr>
<td>Hepatocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Esophageal</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2  Risk of recurrence after blood transfusion (any) based on the level of evidence. The figure illustrates the risk of recurrence associated with blood transfusion according to different cancers. Based on the literature indicates that patients with colorectal cancer have an increased risk of recurrence. This is risk appears to be minimal in patients with prostate cancer.

Although, several studies have shown that perioperative thrombocytosis and thrombocytopenia are an independent prognostic factor for cancer recurrence and reduced survival in cancer patients, it is not clear whether the perioperative administration of PCs is associated with poor oncological outcomes cancer. In a retrospective study, Kaido et al. found that recurrence free survival was shorter in patients with hepatocellular carcinoma who received platelets concentrations during liver transplantation.

Transfusion of fresh frozen plasma

Fresh frozen plasma can be obtained either by isolation from whole blood donation, or obtained by plasmapheresis. It is frequently used to replace coagulation factors in cancer patients with congenital or acquired hemostatic disorders such as disseminated intravascular coagulation, purpura, warfarin-induced coagulopathy, or liver dysfunction. The administration of FFP has also been implicated in TRIM; however, it appears that high volume of FFP are required to induce immune suppression since the amount of molecules such as Fas–Fas ligand that can interact with the host immune cells including NK cells, and cytotoxic T cells are low compared to that measured in pRBCs and PC.

The current evidence is inconclusive to support the notion that the administration of FFP is associated with decreased cancer related survival. Shiba et al. demonstrated that the perioperative transfusion of FFP is a predictor of poor cancer recurrence and overall survival after pancreatic cancer surgery and metastatic liver resections; conversely, Tomimaru et al. could not demonstrate a statistical significant association in patients with hepatocellular carcinoma.

Platelet transfusions

Thrombocytopenia is a common multifactorial complication of cancer; it can be due to splenic sequestration, chemotherapy-induced myelosuppression or immune mediated platelet destruction. The American Society of Clinical Oncology recommends the prophylactic administration of platelet in patients with cancer either solid tumors or hematologic malignancies to achieve a count minimum count of 10,000 cells/µL, although 20,000 cells/µL should be maintained in patients with highly bleeding tumors. In the context of surgery and acute bleeding, the thresholds to initiate the transfusion of PC might be different since a sudden decrease in the count as a result of consumptive coagulopathy or dilution exposes patients to an increase risk of bleeding. Therefore, it is a commonly accepted practice to initiate the administration of platelets when it counts has reach 75,000 cells/µL; although, minimally invasive surgical procedures are frequently done with lower counts.

Platelets appear to be involved in cancer metastasis. Platelets are known for protecting tumor cells either by direct shielding of malignant cells or permitting evasion from NK cells and TNF cytotoxicity, and can also promote tumor growth by the release of biologic response modifiers during storage such as interleukins, chemokines and grow factors which can eventually affect host immune surveillance.

Conclusion

Despite the recent improvements in patient selection and surgical techniques, perioperative anemia, pRBCs transfusions and the administration of PC and FFP area common clinical scenarios in patients undergoing cancer surgery. In this patient population, perioperative anemia appears to be associated to poor oncological outcomes; therefore, its correction is warranted. Unfortunately, the use of blood transfusions to treat anemia might be linked to an increased risk of cancer recurrence in patients with colorectal, lung, hepatobiliary cancers. It remains still unclear whether the perioperative administration of PCs and FFP are independent prognostic factors of poor oncological outcomes; however, due to their potential immune suppressive effect it is appropriate to target their use with caution.

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Conflict of interest

None.
References


