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Review

Red blood cell transfusion and outcome in cancer

Nayyer Iqbal[a,b], Kamal Haider[a,b], Vinita Sundaram[a], Julia Radosevic[c], Thierry Burnouf[d,e,*], Jerard Seghatchian[f,*], Hadi Goubran[a,b,*]

[a] Saskatoon Cancer Centre, Saskatoon, SK, Canada
[b] College of Medicine, University of Saskatchewan, SK, Canada
[c] Human Protein Process Sciences, Aubers, France
[d] Graduate Institute of Biological Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan
[e] International PhD Program in Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan
[f] International Consultancy in Blood Components Quality/Safety Improvement, Audit/Inspection and DDR Strategies, London, UK

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ABSTRACT

Oncology services utilize about 15% of the blood transfusion resources in the USA. Red blood cell transfusion is performed immediately before, during or after major surgery to compensate for blood loss and hemodilution. However, a lack of evidence-based guidelines leads to variable transfusion practices among clinicians. The benefits of transfusing blood products are obvious in life-threatening low blood cell counts or bleeding, but it is becoming apparent that deliberate blood transfusion in some cancer patients can trigger negative clinical impacts. This review attempts to provide an overview of the impact of red blood cell transfusion in patients suffering from various types of oncologic pathologies.

Contents

1. Introduction

Over 85 million units of packed RBC are transfused globally [1]. The oncology services utilize a large percentage of the transfusion resources; in the USA about 15% of these resources are allocated to hematology and oncology [2]. In the absence of evidence based guidelines for transfusion, significant variability is noted in transfusion practices between and even within different treatment centers. The latest AABB guidelines for transfusions set the transfusion threshold between 60 and 90 g/L of hemoglobin depending on clinical judgment [3]. This leads to arbitrary transfusion practices, rather than physiological-necessity-based transfusion. In addition, debate about the impact of the age of the red blood cells on patients' outcomes is still on-going [4].

Cancer patients are commonly transfused with blood components immediately before, during or after major surgery. Blood loss and hemodilution are the most common causes of red blood cell (RBCs) administration and coagulopathies are the indications for the infusion of fresh-frozen plasma (FFP), cryoprecipitate and platelets [5]. Transfusion-related immune modulation is a com-

* Corresponding authors at: Saskatoon Cancer Centre, 20 Campus Drive, S7N 4H4 Saskatoon, Canada.
E-mail addresses: thburnouf@gmail.com, thierry@tmu.edu.tw (T. Burnouf), jseghatchian@btopenworld.com (J. Seghatchian), hadi.goubranmessiha@saskcancer.ca (H. Goubran).

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plication associated with the administration of blood component therapy [6]. A decreased immune surveillance as a consequence of the transfusion of residual viable leucocytes, apoptotic cells, and various biological response modifiers (BRMs) present in packed RBCs has been linked to cancer recurrence and progression [6], whereas platelets, microparticles and FFP may directly stimulate tumor growth and spread [7–9].

Although the benefits of these blood products are not a matter of debate in specific pathological conditions associated with life-threatening low blood cell counts or bleeding, increasing clinical evidence is nevertheless suggesting that deliberate transfusion of these blood components may actually lead to negative clinical outcomes in cancer patients [10]. Further studies addressing the quality impact of blood processing methodologies and aiming at avoiding the accumulation of BRMs should be encouraged to improve the safety of blood components transfused to cancer patients. This review evaluates the current status of knowledge accumulated on the impact of red blood cell transfusion in patients suffering from various cancers.

2. Blood transfusion

2.1. Colorectal cancer and transfusion

Colorectal cancer (CRC) is the second-leading cause of cancer-related death in the US and the second most common cancer in Europe both in terms of incidence and mortality. Approximately 90% of all cancer deaths arise from the metastatic dissemination of primary tumors. Perhaps the earliest observation of the association between cancer recurrence and peri-operative transfusion was made in CRC patients undergoing a curative intent surgery.

Retrospective studies of the relationship between perioperative blood transfusion and colorectal cancer recurrence were reviewed by Tartter [11]. Perioperative blood transfusion was associated with preoperative anaemia, operations for rectal carcinoma, presence of tumor in the right colon, prolonged procedures, and copious blood loss [11]. None of the negative studies had sufficient numbers of both transfused and un-transfused patients to reject the hypothesis that blood transfusion is associated with cancer recurrence with statistical validity and it was therefore suggested that prospective studies are needed to validate this hypothesis [11,12]. In a review of 14 studies on the effect of blood transfusion on recurrence of CRC after surgery, 8 studies concluded that a detrimental effect does exist, while six other studies could not demonstrate it [13].

Furthermore, an increased incidence of postoperative complications and infections were seen in transfused patient undergoing surgery for CRC. Out of the 134 patients who received RBC transfusions, 33 patients (24.6%) developed infectious complications compared with 9 (4.3%) of the 209 patients who were not transfused ($p < 0.0001$) [14]. This issue was revisited in a study on 492 patients undergoing elective CRC resection at the Massachusetts General Hospital between January 1992 and December 1994. The risk of postoperative wound infection increased by 14 percent per unit of red cells transfused ($p < 0.001$) [15].

The first large study aiming at demonstrating the deleterious effect of blood transfusion in CRC patients was conducted on 1221 patients operated for a CRC between 1969 and 1988, 753 patients having undergone a curative surgical procedure with a follow-up of at least six months were evaluated retrospectively. 134 patients (17.2%) did not receive any transfusion; whereas 619 (82.80%) received transfusions including 150 with packed red blood cells only. Prognostic value of transfusions was evaluated with regard of the components and the quantity of transfused components, the time of transfusions, the surgical procedures and the tumor location (colon or rectum). The 5-years survival of transfused patients was less than for non-transfused patients (56.3% vs. 61.7%, $p > 0.05$ NS), but only the transfusions of more than 5 packed red blood cells worsened significantly the prognostic (5 years $chi^2 = 5.7$; $p < 0.02$). The results, therefore, pointed to the fact that transfusions could influence survival after surgery for CRC [16].

In another similar study, conducted in the same year on 473 patients operated radically for CRC, the non-transfused patients had a better 5-year survival rate and the difference was statistically significant [17]. Furthermore, an early meta-analysis reviewed some 20 published studies, representing 5236 patients. The cumulative odds ratios (95 per cent confidence interval) of disease recurrence, death from cancer and death from any cause were 1.80 (1.30–2.51), 1.76 (1.15–2.66) and 1.63 (1.12–2.38) respectively supporting the hypothesis that perioperative blood transfusion is associated with an increased risk of recurrence of CRC and death from this malignancy [18]. Interestingly, in another study on 644 patients undergoing extended lymphadenectomy in conjunction to CRC surgery, such an association could not be demonstrated [19].

A retrospective analysis was also conducted on 1404 CRC patients, including 1223 sporadic CRC (SCRC) patients and 181 hereditary (HCRC) patients. Among them, 701 SCRC and 102 HCRC patients received perioperative blood transfusion. In SCRC group, mortality, local recurrence and distant metastasis rate of transfused patients were significantly higher than non-transfused patients (all $p < 0.05$). In HCRC group, mortality was apparently higher in transfused patients than non-transfused patients ($p = 0.002$). SCRC patients transfused with ≥3 units of blood had significantly higher mortality than patients transfused with <3 Units ($p = 0.006$). Transfused CRC patients had markedly lower 10-year survival rates with increased postoperative mortality, local recurrence rate and distant metastasis [20]. A similar report comparing transfused SCRC and HCRC conducted on 1075 CRC patients, including 936 SCRC and 139 HCRC undergoing surgery l. All patients underwent a 10-years follow-up. In the sporadic group, mortality, local recurrence rate and distant metastases rate of transfused patients were significantly higher than non-transfused patients. The 10-year survival rates were significantly lower in patients receiving blood transfusions compared to non-transfused patients. In the hereditary group, mortality was higher in transfused patients compared to non-transfused patients [21].

The poor prognosis is even more pronounced in the elderly population of CRC undergoing surgery and receiving blood transfusion. In a study on 108 patients, aged 75 and above, receiving blood transfusion in the context of CRC surgery, transfused patients had significantly worse overall survival compared to non-transfused patients. In the multivariate analysis, perioperative transfusion (hazard ratio = 3.16, 95% confidence interval = 1.11–8.98, $p = 0.031$) was the only independent indicator of overall survival [22]. Thirty-six studies covering 12,127 patients were included: 23 showed a detrimental effect of peri-operative blood transfusion (PBT); 22 used also multivariable analyses, and 14 found PBT to be an independent prognostic factor. Pooled estimates of PBT effect on CRC recurrence yielded overall odd ratio of 1.42 (95% CI, 1.20–1.67) against transfused patients in randomized controlled studies [23].

A review and meta-analysis from the UK looked at 55 publications of which 12 were prospective analyses [23]. A total of 12,242 patients received PBT prior to undergoing colorectal cancer surgery. PBT are required in almost 85% of patients undergoing colorectal cancer surgery. The large sample size minimized the type II statistical error. However confounders were identified such as advanced age, rectal tumor localization, advanced Dukes' stage of tumor progression, low preoperative hemoglobin levels, presence of preoperative anaemia and higher blood loss during surgery. All-cause mortality was significantly higher in transfused vs. non-transfused patients (44.6% vs. 34.7%) [24].

Conversely, a propensity score-based analysis suggested that poor oncological outcomes after curative colon cancer resection in