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Review

Reflections on multiple strategies to reduce transfusion in cancer patients: A joint narrative

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ABSTRACT

Transfusion of red blood cells, platelets and plasma is widely used in the management of anemia and coagulopathy in cancer patients undergoing surgery, chemotherapy, and radiation. The decision to transfuse should not be made lightly as exposure to transfused blood, whether from an allogeneic or even autologous source, is not without risk and the long-term effect of blood transfusion on cancer outcomes remains questionable. Recognition of anemia associated with nutritional deficiency should be promptly corrected while avoiding the use of erythropoiesis stimulating agents. Minimizing blood loss and the prompt control of bleeding, coupled with a restrictive transfusion strategy, seem to be a reasonable approach that does not appear to be associated with long-term sequelae. Limiting platelet transfusion to patients with severe hypo-proliferative thrombocytopenia, and implementation of local hemostatic measures, together with the use of fractionated coagulation factor concentrates, as an alternative to frozen plasma transfusion, may reduce the exposure of cancer patients to potentially harmful thrombogenic and pro-inflammatory cellular microparticles. This joint narrative highlights current opinions for minimizing blood usage in patients with cancer.

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1. Introduction

Multiple complex etiologies interplay to cause cancer-related anemia (CRA). Blood loss due to solid tumors or in the context of operative interventions, chemotherapy-induced myelosuppression, functional iron deficiency, erythropoietin deficiency due to renal disease, and marrow involvement by metastatic lesions are examples of causes which contribute to a low hemoglobin (Hb) level in the setting of malignancy [1]. Anemia has been found to occur more frequently in older individuals and data on cancer patients of all ages have shown that the presence of anemia is associated with poorer prognosis and functional status [2]. Furthermore, there is enough evidence suggesting that tumor hypoxia in anemic patients has a negative impact on treatment outcomes in patients with cancer [3].

The most common treatment options for CRA include iron therapy, erythropoiesis stimulating agents (ESAs), and red blood cell (RBC) transfusion. Many clinicians are not familiar or comfortable using intravenous (IV) iron products to treat functional iron deficiency associated with CRA [1]. In addition, safety concerns surrounding ESA therapy may contribute to suboptimal treatment of anemia in CRA. As a result, the option of transfusion remains a cornerstone treatment for CRA.

In current practice, allogeneic red blood cell (allo-RBC) transfusion is often used in three settings:

(a) In the perioperative context, to correct CRA or compensate for blood loss occurring in surgery.
(b) Treatment of chemotherapy-induced CRA.
(c) Prior to radiation therapy, to maximize the effect of treatment.

RBC transfusion is usually based on empiric, arbitrary Hb levels set by organizations or institutions. It is recognized that there is significant variability between organizations, and even among individuals within institutions, in terms of Hb level to trigger transfusion.

Conversely, platelet transfusion is typically utilized as a means to treat hypo-proliferative thrombocytopenia in patients who are bleeding or as a prophylactic measure to reduce the risk of clinically significant bleeding. In chemotherapy-induced or radiation-induced thrombocytopenia, platelet transfusion is used to raise platelet counts to safe levels particularly in patients undergoing invasive procedures or in those requiring anticoagulation therapy. Platelet transfusion is also used in the palliative context to control bleeding in the setting of thrombocytopenia caused by heavy bone marrow infiltration. Platelet transfusion thresholds, again, are often arbitrary [4,5], with a level of $<10 \times 10^9$/L in the absence of bleeding and $<20 \times 10^9$/L in the presence of bleeding [6,7]. Higher thresholds are needed if patients are undergoing interventions like central line insertions, operative interventions and invasive procedures and lumbar punctures [8]. The empiric values of 30×10^9/L and 50×10^9/L are often incorporated in many local center guidelines if prophylactic or therapeutic anticoagulation is administered.

There is little evidence to guide the use of frozen plasma transfusion. In general, plasma is often used to correct coagulopathies and clinically significant bleeding attributable to multiple coagulation factor deficiencies in the setting of hepatic failure or consumptive coagulopathy. This may occur in the context of advanced primary hepatic malignancies, metastatic liver disease, or cancer-associated diffuse intravascular coagulopathy (DIC).

2. Strategies to reduce blood transfusion

Multiple strategies have been suggested to reduce blood component transfusion in cancer patients.

2.1. Autologous red blood cell (auto-RBC) transfusion

The potential risk of disseminating tumor cells by transfusion of autologous blood, collected prior to or in the context of surgery, has historically limited the use of autologous blood in patients with CRA. The concept that transfusion of auto-, rather than allo-BC may be associated with better cancer outcomes has been contemplated by many investigators. In general, patients with cancer are poor candidates for pre-operative blood collection due to their CRA. However, collection and transfusion of auto-RBC collected by intraoperative blood salvage techniques remains a viable option for patients with cancer.

In the setting of major blood loss surgery, transfusion of auto-RBC collected by cell-salvage is associated with non-inferior outcomes compared to traditional intraoperative allo-RBC [9]. Silencing of the gene encoding pi class of glutathione-S transferase is a specific and sensitive molecular marker for prostate cancer. Auto-RBC transfusion safety was demonstrated when no tumor-specific gene amplification was found after RBC collected intraoperatively during radical prostatectomy underwent both filtration and irradiation prior to reinfusion, suggesting a significant reduction of tumor dissemination risk [10].

The use of a small-pore leukoreduction filter during preparation of auto-RBC collected by the intraoperative cell salvage process has been found to be an effective method to remove malignant cells, reducing, hypothetically the risk of metastasis from auto-RBC reinfusion. The primary limitation to additionally irradiating auto-RBC is the availability of an on-site irradiator, leading to a very limited use of this combined strategy [11]. Isovolemic hemodilution with autologous blood collection and reinfusion, on the other hand is rarely used in the perioperative context in cancer patients.

A recent meta-analysis by Li and Yuen (2017) explored the association between peri-operative RBC transfusion (from both autologous and allogeneic sources) and biochemical recurrence-free survival, overall survival (OS) and cancer-specific survival in patients undergoing radical prostatectomy. The meta-analysis included data from 26,698 patients and results showed that auto-RBC transfusion was not associated with biochemical recurrence-free survival ($P = 0.24$), OS ($P = 0.11$), or cancer-specific survival ($P = 0.96$). Allo-RBC transfusion, on the other hand exhibited a significant association with worse biochemical recurrence-free survival, overall survival (OS) and cancer-specific survival, highlighting the importance of blood conservation strategies to reduce allo-RBC transfusion rates [12].

The survival of the 45 patients operated for esophageal carcinoma with nodal involvement who received auto-RBC transfusion was better than that of the 59 patients who received allo-RBC transfusion ($p = 0.0435$). According to logistic regression analysis, allo-RBC transfusion correlated with tumor recurrence in patients with either nodal involvement or a T3–4 lesion [13], confirming previously reported survival benefit with the use of auto-RBC vs allo-RBC transfusion in 120 esophageal cancer patients [14]. In