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Indications for and complications of transfusion and the management of gynecologic malignancies

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Abstract

Anemia, which is highly prevalent in oncology patients, is one of the most established negative prognostic factors for several gynecologic malignancies. Multiple factors can cause or contribute to the development of anemia in patients with gynecologic cancers; these factors include blood loss (during surgery or directly from the tumor), renal impairment (caused by platinum-based chemotherapy), and marrow dysfunction (from metastases, chemotherapy, and/or radiation therapy). Several peri- and intra-operative strategies can be used to optimize patient management and minimize blood loss related to surgery. Blood transfusions are routinely employed as corrective measures against anemia; however, blood transfusions are one of the most overused healthcare interventions. There are safe and effective evidence-based blood transfusion strategies used in other patient populations that warrant further investigation in the surgical oncology setting. Blood is a valuable healthcare resource, and clinicians can learn to use it more judiciously through

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knowledge of the potential risks and complications of blood interventions, as well as the ability to properly identify the patients most likely to benefit from such interventions.

Keywords

gynecologic malignancy; blood transfusion; anemia; cancer

Anemia in the cancer patient

Prevalence and pathogenesis

Secondary to disease progression or as a consequence of treatment, many cancer patients will require blood products at some point during their continuum of care. This need for blood often coincides with the development of symptomatic anemia. According to the World Health Organization, a hemoglobin (Hb) level 12 g/dL (120 g/L) is considered normal in non-pregnant women. Mild, moderate, and severe anemia are identified at Hb levels of 11.0–11.9, 8.0–10.9, and <8.0 g/dL, respectively (1). While numerical cutoffs do not reflect patient comorbidities, which contribute significantly to the variation in symptomatology, they are the main parameters used to guide transfusion practice. More than 6 million units of red blood cells (RBCs) are transfused in the United States annually, at an estimated cost of \$1600–\$2400 per transfusion event (2–4). Oncology patients account for 34% of this blood supply use and cost (5).

Clinicians use low Hb concentration or low hematocrit as the complete blood count parameters to define anemia. Symptoms are dependent upon the degree of anemia and the rate at which it develops. The reduction of Hb concentration to 5 g/dL maintains adequate tissue oxygen delivery in healthy resting adults, with symptoms occurring only when the Hb concentration drops below this level. In the postoperative setting, Hb levels of 7.1–8.0 g/dL have a low risk of death, with the mortality rate rising to 34.4% with Hb levels of 4.1–5.0 g/dL (6). There are several compensatory mechanisms in response to anemia, such as increased heart rate, increased respiratory rate, and a right shift of the oxygen-dissociation curve, all with the goal to maintain adequate oxygen delivery to the tissue. The main symptoms of anemia, such as dyspnea, palpitations and fatigue, are manifestations of these compensatory mechanisms. Functional impairment and a decline in subjective well-being are also highly distressing symptoms that are detrimental to a patient's quality of life and affect their ability to tolerate cancer treatments.

Multiple factors can cause or contribute to anemia in the oncology setting. Patients should undergo a basic work-up to identify possible causes. The work-up should include reticulocyte, creatinine, iron (serum iron, total iron-binding capacity, transferrin saturation, and serum ferritin), B12, and folate measurements (7). Cancer-related anemia (CRA), which can occur in patients with malignancies, is considered a cytokine-mediated process between tumor cells and the immune system, with an overexpression of certain pro-inflammatory cytokines, specifically interleukin-1 (IL-1) and tumor necrosis factor (TNF). These cytokines have been shown to impair iron utilization, suppress erythroid maturation, and reduce erythropoietin (EPO) production (8). In CRA, hepcidin, an iron regulatory peptide, is

upregulated and inhibits the transport of iron via macrophages in the duodenum, decreasing gastrointestinal absorption and the accessibility of stored iron. CRA is typically a normochromic, normocytic anemia associated with a low reticulocyte count.

The European Cancer Anemia Survey (ECAS), which was conducted across 24 European countries and 748 cancer centers, assessed more than 13,600 patients for the incidence and prevalence of anemia across various cancer types and stages of treatment. In the study, anemia was defined as an Hb level <12.0 g/dL. Gynecologic malignancies accounted for 11.6% of all cases. The ECAS found a prevalence of anemia of 39.3% and 67.0% at enrollment and during the survey, respectively. When looking specifically at patients with gynecologic cancers, 48.1% were anemic at enrollment, of which only 42.7% ever received treatment for their anemia (9). In gynecologic malignancies, the most common factors associated with the development of anemia are blood loss (during surgery or directly from the tumor), renal dysfunction (secondary to platinum-based chemotherapy), and marrow dysfunction (from metastases, chemotherapy, and/or radiation) (Figure 1).

Prognosis

In a systematic review assessing anemia as an independent prognostic factor for survival in patients with various cancers, Caro *et al.* noted reduced median survival times of 20% to 43% across cancer types in anemic patients compared to those without anemia, with an overall adjusted HRR of 1.65 (aHRR, 1.19–1.75) (10). Findings from a systematic review by Knight *et al.* showed that nearly all studies reported an association between anemia and decreased survival or increased mortality for multiple cancer types. The authors cautioned that the relationships between anemia and disease progression, treatment response, and overall survival may not be causal, as these findings were based on observational studies (11).

There is abundant evidence establishing anemia as one of the most prevailing prognostic factors in patients with cervical cancer (Table 1) (12–28). Most published studies exploring this relationship are retrospective and include patients who had undergone some form of radiation therapy. This poses a confounder on prognosis, since anemia may predict resistance to radiation (Refer to section: Implications for Radiation Therapy), indirectly impacting survival. Alternatively, anemia may independently characterize more aggressive tumors, representing a surrogate for poor prognosis. It is unclear whether Hb is an independent prognostic factor for outcome or a surrogate for advanced disease. What is clear is that patients with cervical cancer and anemia have shortened survivals.

A retrospective analysis of 61 patients with uterine cancer who had undergone surgical treatment, Metindir *et al.* found that 42.6% of these patients had a pretreatment Hb level <12 g/dL. These patients were more likely to have higher rates of positive cytology and advanced International Federation of Gynecology and Obstetrics (FIGO) stage disease (29). Supporting data were shown by Njolstad *et al.* and Wilairat *et al.*, who found that 5-year disease-free and overall survivals were significantly lower in patients with an Hb level <12 g/dL prior to treatment (30, 31).

The association between anemia and survival in patients with ovarian cancer was demonstrated by Munsted *et al.*, who showed that Hb levels before and during chemotherapy significantly correlated with other important prognostic parameters, such as age at diagnosis, tumor stage, and tumor grade. Hb levels >12 g/dL prior to and during chemotherapy were significantly associated with longer survival (32). Maccio *et al.* found that in 91 patients with epithelial ovarian cancer, pretreatment Hb concentrations were inversely related to stage of disease and Eastern Cooperative Oncology Group (ECOG) performance status. In their analysis, the lowest Hb levels were associated with the highest concentrations of pro-inflammatory markers (IL-6, IL-1 β , and TNF) (33). In a prospective review assessing the relationship of pretreatment serum Hb levels to survival in patients with epithelial ovarian carcinoma, Obermair and colleagues reported overall survival rates of 38.5% and 52.3% in patients with pretreatment Hb levels <12 g/dL and >12 g/dL, respectively (p=0.008) (34). Similar results of recurrence and survival were corroborated by subsequent analyses (35–37).

In a study of 62 patients with vulvar cancer of all stages, of whom 30.6% had anemia, a pretreatment Hb level <12 g/dL was associated with poor prognosis, but failed to show significance on multivariate analysis. The authors suggested that anemia may be a marker for a more aggressive tumor, leading to the early development of metastases (38). In addition to other factors, such as histology and stage, these studies demonstrated the importance of anemia with regard to treatment outcomes.

Implications for chemotherapy

Anemia rates related to the use of chemotherapeutic agents vary widely based on baseline Hb values, type of malignancy, and the type/duration/cycle of chemotherapy (Table 2) (39–41). The incidence and severity of anemia are highest in patients receiving dose-dense paclitaxel-carboplatin therapy. Data from the Japanese Gynecologic Oncology Group (JGOG) study 3016 indicated grade 3–4 anemia in >50% of patients; in the dose-dense arm, 90% of patients had at least one treatment delayed due to anemia (41). Cisplatin treatment is one of the most common causes of chemotherapy-induced anemia, and >40% of patients will develop anemia during treatment with this agent. Hensley *et al.* identified a pretreatment Hb level <10 g/dL as a significant risk factor for transfusion need in patients undergoing therapy with carboplatin-paclitaxel (42). Furthermore, patients with ovarian cancer typically undergo large debulking surgeries, making them even more susceptible to the development of anemia.

The prospective ECAS survey found that patients actively receiving chemotherapy compared to those who were not had the highest incidence of anemia; the rate of anemia increased from 19.5% during the first cycle of chemotherapy to 46.7% after the fifth. Women with gynecologic malignancies receiving chemotherapy had the highest rate of anemia overall (88.3%) in comparison to patients who had breast, lung, colorectal or urogenital cancer; leukemias; or lymphomas (9). The mean Hb to initiate a transfusion in this study was 9.7 g/dL. In a large-scale UK audit of patients with a variety of solid tumors receiving chemotherapy, Barrett-Lee *et al.* noted a mean Hb level drop from 10.7 g/dL with the first cycle of chemotherapy to 9.9 g/dL by the sixth (43). The absolute indication for transfusion

in patients actively receiving chemotherapy is unclear, and often will depend upon chemotherapy type, duration of treatment, and the severity of patient symptoms. Patients rarely require transfusion at Hb levels >9 g/dL, and at our institution, patients are typically transfused once their Hb level falls below 7 g/dL.

Implications for radiation therapy

There is experimental and clinical evidence demonstrating the association between anemia and radiation therapy failure. Whether this is because anemia represents more aggressive disease or whether this is an independent prognostic factor is unclear. In experimental models, anemia was found to be linked to intratumoral hypoxia, and radiation was less effective in these tissues (44). One theory to explain the link between anemia and radiation therapy resistance is that the efficacy of radiation therapy depends on tissue oxygenation and that a decrease in Hb has a more profound effect on tumor tissue compared with normal tissue. Tumor hypoxia, therefore, may confer radioresistance, which subsequently decreases locoregional control and promotes tumor progression (45). Another theory linking anemia with radiation therapy resistance is that tumor hypoxia possibly causes genomic and proteomic changes (i.e., hypoxia-inducible factors 1 α and 2 α) that result in a more 'aggressive' tumor phenotype. Implicit to both theories is that the correction of anemia (and tumor hypoxia) may reverse these negative consequences; however, as previously mentioned, blood transfusions have been reported to decrease survival independently of anemia, making these data difficult to interpret.

There are numerous publications in the cervical cancer literature that have shown the link between anemia and radiation therapy failure. There are also a few retrospective studies that suggest transfusions may improve survival in this patient population. Grogan *et al.* collected data on 605 patients with cervical cancer treated with radiation therapy and found that the average weekly nadir Hb during radiation therapy was significantly correlated with local control, disease-free survival and overall survival, but blood transfusions appeared to overcome the negative prognostic effects of low Hb prior to and during radiation therapy (15). Based on their analysis, the authors suggested maintaining Hb levels to at least >12 g/dL during radiation therapy, which improves both pelvic control and distant metastases. In an analysis of 204 patients with cervical cancer undergoing radiation therapy and treated with regular transfusions to maintain an Hb level >11 g/dL, Kapp *et al.* found that transfused patients had an identical prognosis compared to non-anemic patients without transfusion, suggesting the negative effects of anemia were eliminated through the correction of Hb levels (46). Other groups have reported contradictory findings, showing the use of blood transfusion is not correlated with clinical benefit (12, 20). Although the only prospective study assessing the benefit of correcting Hb levels via blood transfusion in patients with cervical cancer was underpowered for this purpose, the study findings suggested that raising a patient's Hb level to >12 g/dL could decrease the risk of local relapse (47). The National Comprehensive Cancer Network® (NCCN®) currently recommends transfusions to achieve an Hb level >7 g/dL in hemodynamically stable, asymptomatic patients, which is in keeping with our institutional practice (48).

Indications for transfusion

Guidelines from the AABB (formerly the American Association of Blood Banks) provide a framework for guiding transfusion decisions. While few of the studies used to generate the AABB guidelines include gynecologic oncology patients, the main AABB recommendation, which recommends adhering to a restrictive transfusion strategy (< 7 g/dL) in stable hospitalized patients, is in line with the NCCN[®] guidelines (49). According to the practice guidelines of the American Society of Anesthesiologists task force, red blood cell transfusion is rarely indicated when Hb concentration is >10 g/dL, and it is almost always indicated when Hb concentration is <6 g/dL (50). In surgical patients exhibiting symptoms of anemia, transfusion should be considered at an Hb concentration of < 8 g/dL.

Unlike in the critical care and cardiac surgery literature, there is no clear transfusion trigger reported in the surgical oncology and oncology literature. The Transfusion Requirements in Critical Care (TRICC) trial enrolled 838 critically ill patients who were randomly assigned to a restrictive transfusion strategy (Hb <7 g/dL and maintained at 7 to 9 g/dL) or a liberal transfusion strategy (Hb <10 g/dL and maintained at 10 to 12 g/dL). The mortality rate during hospitalization was significantly lower in the restrictive strategy group, suggesting that a restrictive strategy of RBC transfusion was non-inferior, and perhaps superior, to a liberal strategy (51).

The recent Transfusion Requirements after Cardiac Surgery (TRACS) trial showed that the use of a restrictive perioperative transfusion strategy (Hb >9.1 g/dL versus 10.5 g/dL) resulted in non-inferior rates of 30-day all-cause mortality and severe morbidity. The authors also found that the number of transfused RBC units, irrespective of the liberal versus restrictive approach, was an independent risk factor for clinical complications or death at 30 days (52). Findings from the CRIT study showed similar results, i.e., that the number of RBC units transfused in the critically ill is an independent predictor of worse clinical outcome. The authors also noted that despite data regarding RBC transfusion thresholds and risks, practice patterns in the United States have not significantly changed (53).

In patients at high risk for anemia following hip surgery, researchers found that a liberal transfusion strategy (<10 g/dL) compared to a restrictive strategy (<8 g/dL) did not result in a decreased rate of death and in-hospital complications. The authors recommended withholding transfusions in the absence of symptomatic anemia, even in elderly patients with concomitant cardiovascular disease (54). The Transfusion Requirements in Septic Shock (TRISS) trial similarly found that in patients with septic shock, those who underwent a transfusion at an Hb threshold of 7 g/dL had similar 90-day mortality, use of life support, and number of days alive compared to those who underwent transfusion at 9 g/dL (55).

A recent Cochrane review, which included more than 6200 patients, found that a restrictive transfusion strategy did not impact the rate of adverse events, was associated with a significant reduction in hospital mortality, and did not impede functional recovery (56). In these critically ill patients, a restrictive transfusion approach is non-inferior to a liberal one.

The only prospective trial to assess transfusion requirements in surgical oncology patients randomized oncology patients who had undergone abdominal surgery to either a restrictive

(<7 g/dL) or liberal (<9 g/dL) transfusion strategy. Unlike the TRICC, TRACS and CRIT studies, de Almeida and colleagues randomized 198 critically ill patients admitted to the surgical intensive care unit (ICU) after surgery and found that a liberal transfusion strategy was superior in terms of the primary outcome, 30-day mortality or severe clinical complications (major cardiovascular events, intra-abdominal infections). There were no differences in the rates of septic shock, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), ICU admissions, or length of hospital stay. The study lacks long-term follow-up data, which may have important implications in terms of recurrence rates (57).

Boone and colleagues recently examined outcomes in patients with gynecologic malignancies after their center implemented a restrictive policy (transfusion of one RBC unit at a time with an Hb level <7 g/dL). Although this was a retrospective analysis, they found that morbidity and mortality were not increased with the introduction of a restrictive transfusion policy (58). Despite the abundant literature to support lower transfusion thresholds, a survey of Society of Gynecologic Oncology members reported by Price *et al.* showed that 44% of respondents favored a postoperative transfusion trigger of Hb 8 g/dL, but 32% chose a trigger of Hb 9 g/dL. Furthermore, most physicians indicated they would still transfuse two units at their respective thresholds, with the level of anemia not influencing the decision on how much blood to transfuse. The reason why these clinicians chose to administer 2-unit transfusions was unclear, which is indicative of how these decisions are often reflexive rather than individualized to the patient (59). This discord may be due to a lack of prospective trials evaluating transfusion parameters within the oncology setting, as well as the lack of published guidelines specific to this patient population.

Risks associated with blood transfusion

While one of the most efficient ways to correct anemia is through a blood transfusion, 20% of all transfusions lead to an adverse event, with serious complications occurring in ~0.5% of transfusions. The more common complications associated with blood transfusions are discussed in detail below, and a comprehensive review of these complications is provided in a review by Delaney *et al.* (60).

Transfusion reactions

Transfusion reactions are generally categorized as acute (within 24 hours of the transfusion) or delayed (>24 hours after the transfusion), and then further classified depending on whether or not fever is present. Acute reactions presenting with fever are acute hemolytic, febrile non-hemolytic, or a transfusion-related acute lung injury (TRALI). Acute hemolytic reactions are characterized by symptoms and laboratory findings of acute intravascular hemolysis (decreased haptoglobin, increased serum lactate dehydrogenase [LDH], increased indirect bilirubin, hemoglobinuria, and hemoglobinemia). Symptoms usually appear within minutes of starting the transfusion. The most common cause of an acute hemolytic reaction is ABO incompatibility, which almost always stems from medical errors occurring outside of the laboratory.

Acute febrile non-hemolytic transfusion reactions (FNHTRs) are usually attributable to the recipient's response to residual donor leukocytes or cytokines in the plasma of the transfused

product and are most often seen with the use of cellular blood products (RBCs, platelets). The reaction is defined as a rise in the patient's temperature of 1°C during or shortly after completing the transfusion that cannot be attributed to the patient's underlying condition or any other cause. Pre-storage leukocyte reduction within 72 hours of collecting the blood product removes >99% of the donor leukocytes, which significantly reduces the incidence of FNHTR.

Allergic transfusion reactions are quite common and most often manifest as mild, localized urticaria and pruritus without fever. Systematic symptoms, such as bronchospasm, nausea, vomiting and diarrhea, are also occasionally reported. The reactions occur when a transfusion recipient has preformed immunoglobulin E (IgE) antibody against an antigen in the donor plasma. Most allergic reactions respond to antihistamines, while more severe reactions/anaphylaxis may require steroids or epinephrine. Premedication with antihistamines and corticosteroids should be considered prior to subsequent transfusions only when there is a history of repeat reactions.

Lung injury

Transfusion-related acute lung injury (TRALI), which is an acute respiratory distress syndrome that occurs within 4–6 hours of a transfusion, occurs at a rate of 8.1 per 100,000 transfused components. TRALI is considered a reaction between donor leukocyte antibodies and recipient antigens, causing a downstream, cytokine-mediated interaction between neutrophils and the lung endothelium. This ultimately leads to increased microvascular permeability and pulmonary edema. Clinically, it is characterized by non-cardiogenic pulmonary edema, leading to dyspnea and hypoxemia. TRALI is the most common cause of transfusion-related fatalities, but it is often under-recognized and under-reported. As such, a consensus committee established criteria for the clinical diagnosis of TRALI (Table 3) (61).

Transfusion-associated cardiac overload (TACO) is a common complication of blood transfusions, occurring at a rate of 1–11 per 100 RBC units transfused. Recent surgery and female gender are risk factors for the development of TACO (62). The clinical presentation of TACO includes signs of fluid overload (elevated systolic blood pressure, elevated jugular venous pressure, and pulmonary edema), dyspnea, tachypnea, and an elevated B-natriuretic peptide level. Diuresis usually leads to rapid improvement in symptoms, and fatality rates are low. A TACO diagnosis can be confirmed by the finding of new, acute pulmonary edema or vascular congestion on a chest x-ray. In high-risk patients, the development of TACO can be prevented by implementing transfusions of one unit of RBCs at a time, at a rate of 4 mL/minute (2 hours for RBCs, 3–4 hours for whole blood) (63). A diuretic before or during the transfusion may be considered in patients at greatest risk for volume overload to prevent this complication.

Immunomodulation and tumor recurrence

Allogeneic blood transfusion-related immune modulation (TRIM) is a phenomenon initially described in the renal transplant literature. Opelz *et al.* showed that recipients of allogeneic blood transfusions had improved renal allograft survival. Given these findings, allogeneic transfusions were administered routinely as an immunosuppressant in an attempt to prevent

or delay renal allograft rejection in renal transplant patients (64). Gantt later reported that the immunosuppressive effect that is beneficial to transplant patients may be deleterious in cancer patients (65). Since then, several hundred studies on the increased risks of postoperative infections and cancer recurrence in patients receiving blood transfusions have been published (66). Although the exact mechanisms underlying TRIM continue to be debated, some researchers postulate that mechanisms suppressing host natural killer cells and activating suppressor T-lymphocytes are involved (67).

An analysis of more than 20,000 patients with colorectal cancer found that allogeneic blood transfusion was associated with an increased odds ratio (OR) of 1.66 for recurrence (95% CI, 1.1–1.97) and 1.45 (95% CI, 1.19–1.46) for cancer-related mortality (68). In gynecologic malignancies, De Oliveira *et al.* found an association between recurrence risk and allogeneic blood transfusion in patients with epithelial ovarian cancer undergoing optimal cytoreductive surgery. Time to recurrence was 17 months in patients who had undergone a transfusion compared with 11 months for those who had not ($p=0.03$) (69). In cervical cancer, Azuma *et al.* found that after correcting for other factors, patients with stage IB cervical cancer who had not undergone a perioperative transfusion had a much higher survival rate than those who had undergone a transfusion (70). A series by Monk *et al.*, showed that perioperative blood transfusions did not impact overall survival or time to recurrence in patients with stage IIA cervical cancer (71). Taken together, these data suggest that exposure to allogeneic transfusions should be minimized in these patients.

The immunomodulatory mechanisms of transfusions may also affect the rate of postoperative bacterial infections. There have been several randomized controlled trials investigating the association between perioperative blood transfusions and postoperative bacterial infections. A recent review of 18 randomized trials found that among hospitalized patients, a restrictive RBC transfusion strategy was associated with a reduced risk of lung and wound infections, pneumonia, and sepsis (72). In a systematic review and meta-analysis of patients who had undergone surgery for colorectal cancer, the OR for developing postoperative infection following a transfusion was 3.27 (2.05–5.20) (68). Bernard *et al.* found that one unit of RBCs significantly increased the risk of pneumonia (OR, 1.24) and sepsis (OR, 1.29), and that transfusions with two units increased this risk by an additional 1.25 and 1.53, respectively (73).

Peri- and postoperative blood transfusions also have been associated with an increased risk of venous thromboembolism (VTE), higher composite morbidity, mortality, and length of hospital stay (3, 74).

Infectious risk

Infectious pathogen transmission is a less-common risk in patients undergoing blood transfusion, but it can pose a serious health risk nonetheless (Table 4). Over the last 30 years, there have been huge improvements to ensure the safety of modern blood products. The introduction of nucleic acid testing (used to detect human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and West Nile virus) and the bacterial screening of platelets has hugely reduced the transmission of these pathogens. The approach to the safety of the blood supply, however, has remained largely reactive. When an emerging infectious agent (e.g.,

Zika, Dengue, Chikungunya) is identified as a risk to the blood supply, a new test to detect the agent must be developed, tested, and Food and Drug Administration (FDA) approved for widespread use. During this time, transfusion recipients may be at serious risk for infection. The need for a proactive strategy towards blood safety led to the development of pathogen inactivation (PI) technology.

While PI of blood products has been used extensively in Europe for many years, it has only recently been FDA approved in the United States. The basic concept behind PI technology is to inactivate, rather than remove or reduce, any pathogens that are present in the blood product, and prevent these pathogens from growing or reproducing, rendering them non-infectious. There are several such technologies available, but currently, only the INTERCEPT™ blood system (Cerus Corporation, Concord, California) is FDA cleared for use in plasma and platelets (75).

The INTERCEPT™ system uses a psoralen (amotosalen), which intercalates between the nucleotide base pairs of any DNA or RNA present in the blood product. The product is then photo-activated with UV-A light, which leads to the irreversible cross-linking of nucleic acids. Any remaining psoralens and photoproducts are removed prior to infusion by a charcoal filter (76). Within the platelet products, the DNA and RNA of residual white blood cells are also damaged. PI products do not need to be irradiated for graft-versus-host disease prevention. The advantage of the nonspecific targeting of all nucleotide base pairs is that unknown infectious organisms can be targeted before they are even identified. For example, studies have shown that INTERCEPT™ technology was effective against the Dengue, Chikungunya, and West Nile viruses even before they were identified in the US blood supply (77). The system's extensive use in Europe has given credence to its safety, as there has not been an increase in reported adverse events associated with this product in comparison with conventional plasma-containing products (78).

The side effects associated with PI-treated platelets include a small amount of platelet loss, which leads to lower platelet recoveries and post-transfusion count increases, as well as minor decreases in *in vivo* platelet survival (76). Data from clinical studies, however, have not shown increased rates of significant bleeding in patients who receive PI products compared with conventional products (79). Plasma-treated PI has shown some decrease in clotting factors, but its functional activity remains well within the accepted range, making it acceptable for therapeutic use (76). The effects of PI on RBCs are not as well characterized but will most likely include increased RBC loss and decreased storage time (80). Despite the adverse effects of PI on blood products, the safety and risk mitigation it provides the blood supply far outweigh the minor drawbacks.

Peri-operative management of anemia

The diagnosis of anemia should be made via a screening complete blood count, ideally 3–4 weeks prior to a planned surgical procedure. This allows for adequate time to work up the underlying cause of anemia and complete a course of treatment. Potential adjunct treatments of anemia are discussed below.

Iron replacement

Iron deficiency is a common cause of anemia in oncology patients. Iron replacement is an inexpensive and readily available therapeutic option. Two prospective studies in gynecologic oncology found that intravenous (IV) iron is a well-tolerated primary prevention strategy for blood transfusions in patients with ovarian cancer receiving platinum/taxane chemotherapy. Patients randomized to receive IV iron with each cycle of chemotherapy had a higher nadir Hb level, which occurred later in the treatment course, and required fewer total RBC transfusions during the study period (81, 82). Similar reductions in transfusions were observed in patients treated with IV iron while undergoing chemoradiation therapy for cervical cancer (83).

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESAs) are approved for the treatment of anemia associated with chemotherapy. In numerous studies, ESAs have been shown to reduce the need for blood transfusions and improve quality of life in patients with cancer (84–86). The American Society of Clinical Oncology (ASCO) and the American Society of Hematology recommend epoetin or darbepoetin for patients with chemotherapy-associated anemia and an Hb level <10 g/dL, with the goal to raise Hb concentrations to (or near) 12 g/dL (87). An increase in Hb levels is often seen 4–6 weeks after therapy, and the magnitude of the Hb increase is often greater if IV iron is used in combination with an erythropoietin (EPO) (88). Dousias *et al.* evaluated the effects of EPO when administered prior to radical surgery for cervical, ovarian, or endometrial cancer; they concluded that EPO significantly increased Hb levels, leading to the need for fewer blood transfusions (89). In several large multi-center trials, patients with ovarian cancer given EPO while undergoing platinum-based chemotherapy required fewer blood transfusions (90, 91).

Despite the efficacy of ESAs in reducing the need for blood transfusions, there are several reported risks. Two large meta-analyses reported an increased risk of mortality and thromboembolic events, and perhaps shorter overall survival, in patients who received these agents (92). Whether the thrombotic risk is directly linked to the biological action of the ESAs or is mediated by an increase of the red blood cell mass is unknown. Available data suggest that standard doses of EPO substantially affect primary and secondary hemostasis, triggering blood coagulation and inducing a moderate elevation of platelet counts and hyperactivity (93). Numerous authors have cautioned that treatment with ESAs in patients with cancer increases mortality risk and worsens overall survival, and multiple studies have linked EPO with tumor progression (94). The increased risk of death associated with these drugs should be balanced against their benefits (95).

The Southwest Oncology Group (SWOG) conducted a phase II trial to assess the safety of EPO treatment to correct anemia in patients undergoing chemoradiotherapy for stage IIB–IVA cervical cancer. The SWOG reported a mean 1.4 g/dL increase in Hb from the start of treatment to the completion of chemoradiotherapy, but also a higher rate of deep vein thrombosis (DVT) and lower progression-free and overall survivals compared to those of historic controls. The authors were unable to determine whether this was the result of EPO treatment or a lower baseline Hb (96). Gynecologic Oncology Group (GOG) study 191, a

phase III trial to assess EPO use in anemic patients undergoing concurrent radiation and cisplatin therapy for cervical cancer, was closed prematurely due to concerns of high thromboembolic risk associated with EPO (97).

The AGO/NOGGO trial, which had a primary endpoint of 5-year disease-free survival, looked at ESA use in patients undergoing chemotherapy and radiation. The findings of the trial showed that in patients undergoing chemoradiotherapy for cervical cancer, ESA use did not lead to an increase in the rate of thrombosis, and there was no statistically significant difference in survival between patients who did and did not receive EPO (98).

For 10 years, the FDA required that prescribing professionals partake in the ESA Risk Evaluation and Mitigation Strategy (REMS), attesting to their understanding that ESAs shorten overall survival and/or increase the risk of tumor progression or recurrence in patients with certain cancers. In April 2017, the FDA determined that the ESA REMS was no longer necessary. Nevertheless, ASCO cautions that, while the REMS is no longer in place, the serious risks of shortened overall survival and/or increased risk of tumor progression/recurrence associated with these drugs remain. The prescribing information of these agents remains unchanged and notes an increased risk of death, venous thromboembolism, and stroke.

The NCCN[®] recently published Cancer- and Chemotherapy-Induced Anemia guidelines, which contain algorithms to weigh the risks of ESA use (namely increased thrombotic events, possible decreased survival, and shortened time to tumor progression) against those of RBC transfusions. The NCCN[®] suggests considering ESA use in patients with chronic kidney disease, those undergoing palliative treatment, those undergoing myelosuppressive chemotherapy without other causes of anemia, and in those who refuse blood transfusions (48).

Intraoperative management and prevention of blood loss and anemia

Acute normovolemic hemodilution

Patients with normal Hb levels entering surgery or who have been optimized prior to surgery may be candidates for acute normovolemic hemodilution (ANH). ANH is used in patients at high risk for blood loss and is performed immediately before surgery. The procedure consists of removing whole blood from the patient and replacing it with crystalloid/colloid in order to restore euvolemia and render the patient hemodilute during the surgery. During the procedure, the patient's "blood loss" is a diluted version of their original starting whole blood. Once hemostasis is obtained, and toward the end of the procedure, the whole blood collected at the start of the procedure is re-infused into the patient. While ANH has been explored in non-gynecologic oncology patients, data specific to gynecologic surgery are lacking (99). A trial to explore ANH in the gynecologic oncology setting is currently under way.

Cell salvage

The purpose of cell salvage is to reduce or eliminate the need for allogeneic blood transfusions by recovering blood from the surgical field, and then cleaning, filtering, and re-

infusing it into the patient. Circulating tumor cells in cell saver reinfusions have been reported in several cancer types, however, and theoretically, these cells can potentially lead to metastases. Studies of cell salvage during urologic and hepatic oncology surgeries have shown no increase in metastases or mortality (100). In a retrospective analysis of 156 patients who had undergone radical hysterectomy for cervical cancer, Mirhashemi *et al.* found no difference in the rates and patterns of recurrence between patients who had undergone cell salvage and those who had not (101). Connor *et al.* found that the use of cell salvage significantly reduced the need for intraoperative and postoperative blood transfusions in patients with uterine cancer, with no evidence of early disease recurrence at 2-years' follow-up (102). The findings of a prospective study assessing cell salvage in patients undergoing radical hysterectomy for cervical cancer showed no evidence of tumor cell re-infusion, increased recurrence risk, or compromised survival after 16 years of follow-up (103). There are no data to contradict the use of blood salvage in malignant surgery, whereas there are substantial data suggesting worsened outcome when allogeneic transfusions are used (104).

Tranexamic acid

Tranexamic Acid (TxA) works by displacing plasminogen from fibrin, resulting in the inhibition of fibrinolysis. It is typically used to treat menorrhagia but has many off-label uses as well. It also has been used more often in recent years. In surgical oncology patients, two randomized controlled trials have evaluated the efficacy of TxA in preventing blood loss. Results from the first study showed that intraoperative treatment with low-dose TxA reduced intraoperative blood loss in patients undergoing prostatectomy for prostate cancer. There was no increase in the rate of thromboembolic events (at 6 months' follow-up) (105). Findings from the second study showed that a single dose of TxA given before surgery significantly reduced blood loss and transfusion rates in women undergoing radical debulking for presumed ovarian cancer. The study, however, was insufficiently powered to detect differences in complications (106).

Reduced laboratory-associated blood loss

A key means of preventing blood loss, at any time during patient care, is to limit the amount of iatrogenic loss associated with laboratory testing. There are a number of methods by which to accomplish this, including using pediatric collection tubes, avoiding "discard" blood volume when drawing off lines with in-line flush devices, and most importantly, minimizing unnecessary tests and blood cultures. Many institutions have developed interdisciplinary teams that review test utilization on a routine basis. As part of quality improvement initiatives, these teams work with laboratory medicine and information technology services to optimize order sets and order entry alerts to decrease test overutilization.

Management of coagulopathy

Patients with known exposures to anticoagulants or antiplatelet drugs should be evaluated by a hematologist before surgery. An algorithm should be established for the management and monitoring of these patients during and after surgery. Basic conditions of coagulopathy management (e.g., body temperature, pH, ionized calcium) should be optimized prior to the

use of blood products. The use of prothrombin complex concentrates, TxA, and point-of-care testing (viscoelastic methods) to direct the administration of products should be considered. The use of platelet aggregation testing can provide insight into platelet function; if platelet function is suboptimal, the patient may require a platelet transfusion or treatment with vasopressin.

Patient-centered transfusion strategies

Each hospital should have a patient blood management (PBM) program, with clearly defined transfusion thresholds for each blood product that take into account a patient's individual clinical risk factors, symptoms, and anemia tolerance. PBM programs should focus on perioperative anemia management, coagulopathy management, blood conservation strategies, patient-centered transfusions, and patient outcome metrics. As transfusions continue to be one of the most overused interventions in US healthcare, hospital staff should be routinely educated on transfusion triggers. At our institution, an interdisciplinary committee has created transfusion guidelines in an effort to promote the judicious use of blood, cut down on the number of unnecessary transfusions, reduce adverse transfusion events, improve patient care, and conserve limited resources. According to these guidelines, transfusions are recommended in hemodynamically stable patients at a pre-/perioperative Hb level <7 g/dL or postoperative Hb level <8 g/dL. A one-unit transfusion is standard practice, and requesting 2 units requires justification. The implementation of a single-unit policy, followed by a reassessment of the patient, has been shown to improve blood utilization (107). Table 5 provides a brief summary of transfusion guidelines by blood component (108, 109).

Blood alternatives

In rare cases, patients cannot be given conventional blood products; this may be due to choice or for religious reasons. In other cases, a patient may have a rare blood type for which compatible blood cannot be found. Many artificial blood products have been studied but have been pulled from the market due to serious adverse effects (e.g., death, acute myocardial infarction). A hemoglobin-based oxygen carrier (HBOC) is currently being studied in phase I/II clinical trials and remains in production ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02754999): NCT02754999). This HBOC is a pegylated bovine dual-action CO-releasing/oxygen transfer agent. Its functional components (CO, bovine hemoglobin, and polyethylene glycol) inhibit vasoconstriction, decrease RBC extravasation, limit reactive oxygen species production, enhance blood rheology, and deliver oxygen to tissues. Free hemoglobin is extremely toxic and scavenges nitric oxide (NO), which likely accounts for the severe side effects seen with previous generations of HBOCs. However, this product is pegylated and conjugated to CO, which prevents the NO scavenging. In patients with no other options, this product provides life-saving oxygen delivery support while the patient's marrow produces new red blood cells.

The first human immortalized adult erythroid line, providing a potentially sustainable supply of erythroid cells with fewer infectious complications, has been generated recently. These

cells have only been studied in mice so far, but the results have been positive, and this may be a viable alternative to donor blood in the future (110).

Conclusions

Blood transfusions are often used in patients with gynecologic malignancies; however, there has been minimal research and data to guide blood transfusion practices in this patient population. For now, clinical practice in this setting is mainly guided by anecdotal experience rather than published guidelines or data from randomized controlled trials. The indications for the administration of blood products should be to improve tissue oxygen delivery and quality of life. The transfusion trigger for this population remains undefined, and as such, protocols created by a multidisciplinary team are needed. The link between transfusion, prognosis, and recurrence is provocative but confounding, and should caution the surgeon's decision-making. Restrictive blood transfusion strategies have been proven to be safe in several critical care settings. In light of the limited evidence-based data in gynecologic oncology, clinicians should exercise prudence in deciding which patients should undergo transfusion until well-designed trials can provide effective recommendations.

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Highlights

- We review the incidence and prognosis of anemia in the cancer patient
- We present indications and risks for red blood cell transfusion
- We describe peri- and intra-operative management of blood

Figure 1. The multi-factorial pathogenesis of anemia in the cancer patient
 IL-1 – Interleukin 1; TNF – tumor necrosis factor; EPO – erythropoietin

Table 1

Outcomes related to disease progression in patients with cervical cancer and anemia

Authors	Study Design	Number of participants (n)	Stages of Disease	Population	Significant findings
Kapp <i>et al.</i> , 1983	Retrospective	910	IB–IVB	Most EBRT + IVRT	Low hematocrit (<37%) associated with lower OS and DFS, $p=0.027$ and $p=0.01$, respectively
Girinksi <i>et al.</i> , 1989	Retrospective	386	IIB–III	EBRT +/- IVRT	Pretreatment Hb levels (<10 g/mL versus ≥ 10 g/mL) prognostic for local and distant recurrence, $RR = 1.8$ ($p<0.01$)
Pederson <i>et al.</i> , 1995	Retrospective	424	IIB–IVA		Pretreatment Hb levels (value unspecified) prognostic of OS, $RR = 0.88$ (95% CI 0.80–0.96; $p=0.008$); local recurrence, $RR=0.85$ (95% CI 0.75–0.96, $p=0.01$); and distant metastases, $RR = 0.79$ (95% CI 0.69–92, $p=0.003$)
Wernerswasik <i>et al.</i> , 1995	Retrospective	125	I–II	EBRT + IVRT	Risk of recurrence increased linearly with decreasing Hb level (OR 2.02; $p=0.01$)
Grogan <i>et al.</i> , 1999	Retrospective	605	IB–IVA	RT +/- chemotherapy	Pretreatment Hb levels (<120 g/L) prognostic of survival only on univariate analysis; average weekly nadir Hb predictive of OS on multivariate analysis ($p<0.0001$)
Haensgen <i>et al.</i> , 2001	Prospective	70	IIB, IIIB, IVA	Most EBRT + IVRT	Pretreatment Hb level <11 versus ≥ 11 ; 3-yr OS, 27% vs. 62% ($p=0.006$)
Thomas, 2001	Retrospective	605	IB–IVA	Definitive RT	Significant stepwise increase in OS average weekly nadir Hb levels increased ($p < 0.0001$)
Obermair <i>et al.</i> , 2001	Retrospective	57	IB–IVA	Chemo-RT	Hb nadir was the only statistically significant prognostic factor for pelvic failure ($p = 0.029$); severity of anemia during chemo-RT correlated with likelihood of treatment failure
Dunst <i>et al.</i> , 2003	Prospective	87	IIB–IVA	EBRT + IVRT	Pretreatment Hb level <11 g/dL associated with significantly poorer OS ($p=0.003$)
Yalman <i>et al.</i> , 2003	Retrospective	257	II–IVA	Definitive RT	Pretreatment Hb levels (<12.5 g/dL) prognostic of local PFS but not OS on multivariate analysis ($p=0.04$ and $p=0.151$)
Winter <i>et al.</i> , 2004	Retrospective	494	IIB–IVA	Chemo-RT	Average weekly nadir Hb levels ≥ 12 g/dl associated with PFS of 73% versus 40% for those with Hb <10 g/dl ($p<0.0001$); Hb during last third of treatment most predictive of PFS
Fuso <i>et al.</i> , 2005	Retrospective	73	IB2–IIB	NACT + surgery	Optimal response to chemotherapy significantly determined by pretreatment Hb levels ≥ 12 mg/dL, $HR = 6.83$ (95% CI, 2.16–21.60; $p=0.001$)
Grigine <i>et al.</i> , 2007	Retrospective	162	II–III	EBRT+IVRT	Pretreatment Hb level (<120 g/L) associated with decreased OS, $HR = 0.35$ (95% CI 0.18–0.67; $p=0.001$) and DFS, $HR = 0.41$ (95% CI 0.18–0.91; $p=0.04$)
Mayr <i>et al.</i> , 2009	Prospective	88	IB2–IVA	Chemo-RT	Pretreatment Hb and nadir Hb correlated only with local control ($p = 0.039$ and $p = 0.026$, respectively) but not with DSS. Median Hb during treatment (<11.2 g/dL versus ≥ 11.2 g/dL), was prognostic of the 5-year local control, 91% versus 70% ($p = 0.013$)

Authors	Study Design	Number of participants (n)	Stages of Disease	Population	Significant findings
Endo <i>et al.</i> , 2014	Retrospective	85	I–IVA	Concurrent chemo-RT (EBRT+IVRT)	Pretreatment Hb level (<120 g/L) prognostic of OS only on univariate analysis; HR = 1.972 (95% CI, 0.97–4.00)
Shin <i>et al.</i> , 2014	Retrospective	805	IB–IIA		Higher pretreatment Hb prognostic of improved DFS, HR = 0.88 (95% CI, 0.078–0.99) but not of overall survival, HR = 0.94 (95% CI, 0.80–1.10)
Bishop <i>et al.</i> , 2015	Retrospective	2454	IA–III	Definitive RT	Pretreatment Hb measures were not correlated with any outcome endpoint. Minimum Hb level <10 g/dL during treatment was significantly associated with lower DSS (HR = 1.28; 95% CI 1.04–1.58)

EBRT, external beam radiation therapy; IVRT, intravaginal radiation therapy; NACT, neoadjuvant chemotherapy; OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; H, hazard ratio; R, risk ratio; OR, odds ratio; CI, confidence interval

Table 2

Reported incidence of anemia associated with chemotherapeutic agents

Agent(s)	Grade 1, 2	Grade 3, 4
Cisplatin	8%	11%
Carboplatin	66%	7–26%
Docetaxel	73–85%	2–10%
Paclitaxel	93%	0–12%
Topotecan	67%	30–40%
Gemcitabine	8–63%	2–5%
Cisplatin + etoposide	59%	16–55%
Cisplatin + paclitaxel	45–60%	5–25%
Carboplatin + paclitaxel	10–59%	3–34%
Dose dense paclitaxel + carboplatin	5–90%	10–57%

Table 3

Canadian Consensus Conference TRALI diagnosis criteria

<ul style="list-style-type: none">• New onset of ALI• Hypoxemia: PaO2/FiO <300 mm Hg or SPO 90% on RA or other clinical evidence of hypoxemia• Bilateral infiltrates on frontal CXR• No evidence of circulatory overload• Symptoms occur during or within 6 hours of transfusion• No pre-existing ALI before transfusion• No temporal association to alternative risk factors for ALI
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TRALI, transfusion-related acute lung injury; ALI, acute lung injury

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Table 4

Transfusion-associated risk of viral transmission

Virus	Risk
Human Immunodeficiency Virus	1 in 1,466,671
Hepatitis C Virus	1 in 1,148,628
Hepatitis B Virus	1 in 292,561
Human T-cell Lymphotropic Virus	1 in 2,678,836

Table 5

Indications for transfusion of blood product components

Indication
Platelets ($\times 10^9/L$)
<ul style="list-style-type: none"> • <10, provide prophylactic platelet transfusion • <50, transfuse platelets immediately before epidural anesthesia • <50, transfuse platelets where >500 mL expected blood loss • <20, transfuse platelets for procedures not associated with significant blood loss • 20–50, transfuse platelets if significant bleeding during a procedure
Fresh-Frozen Plasma
<ul style="list-style-type: none"> • Indicated in patients with INR, PT or PTT more than $1.5\times$ normal, with bleeding or prior to an invasive procedure • Four-Factor Prothrombin Complex Concentrate should be used for urgent warfarin reversal
Cryoprecipitate
<ul style="list-style-type: none"> • Contains factor VIII, fibrinogen and von Willebrand factor • Used in massive bleeding in patients with fibrinogen <1.5 g/L
Albumin (5% and 25%)
<ul style="list-style-type: none"> • No evidence to support the use of albumin in patients with malignant ascites post-paracentesis • Albumin is not superior to crystalloid for hypoalbuminemia