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Anemia and Transfusions in Patients Undergoing Surgery for Cancer

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Preoperative, operative, and postoperative factors may all contribute to high rates of anemia in patients undergoing surgery for cancer. Allogeneic blood transfusion is associated with both infectious risks and noninfectious risks such as human errors, hemolytic reactions, transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, and transfusion-related immune modulation. Blood transfusion may also be associated with increased risk of cancer recurrence. Blood-conservation measures such as preoperative autologous donation, acute normovolemic hemodilution, perioperative blood salvage, recombinant human erythropoietin (epoetin alfa), electrosurgical dissection, and minimally invasive surgical procedures may reduce the need for allogeneic blood transfusion in elective surgery. This review summarizes published evidence of the consequences of anemia and blood transfusion, the effects of blood storage, the infectious and noninfectious risks of blood transfusion, and the role of blood-conservation strategies for cancer patients who undergo surgery. The optimal blood-management strategy remains to be defined by additional clinical studies. Until that evidence becomes available, the clinical utility of blood conservation should be assessed for each patient individually as a component of preoperative planning in surgical oncology.

Key Words: Anemia—Transfusion—Preoperative autologous donation—Acute normovolemic hemodilution—Perioperative blood salvage—Recombinant human erythropoietin.

A 65-year-old woman with biopsy-proven pancreatic adenocarcinoma and resectable disease was successfully stented. She needs an operation, but her preoperative hemoglobin is 9.5 g/dL.

A 75-year-old man underwent an uncomplicated left hemicolectomy for a T3N1M0 adenocarcinoma of the colon. He has done well postoperatively, except for a slow decrease in his hemoglobin from 10.9 g/dL in the recovery room to 7.3 g/dL on postoperative Day 5. The patient has no signs of bleeding and a history of well-controlled coronary heart disease.

A 68-year-old woman underwent an uncomplicated distal gastrectomy for a T2N0M0 adenocarcinoma. She was discharged to home on postoperative Day 6. She presents at her 4-week postoperative visit with complaints of fatigue and hemoglobin of 8.0 g/dL.

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These three examples highlight the major types of perioperative anemia in patients with cancer who undergo surgery: preoperative, operative, and postoperative. Operative blood loss is an obvious

cause of anemia in surgical oncology, particularly if the surgical procedure is complex[1,2] or the duration of surgery is long.[3,4] However, it is important to note that anemia of chronic disease, nutritional deficiency, and chemotherapy are major contributors to anemia prior to surgery. In addition, tumor location[5] and tumor stage[1,2,5] may influence the risk of preoperative cancer-related anemia. Postoperatively, anemia can be exacerbated by adjuvant chemotherapy or radiotherapy.

The reported prevalence of perioperative anemia in patients undergoing surgery for cancer ranges approximately from 25 to 75%.[6] A systematic review of >100 chemotherapy trials concluded that up to 50–60% of patients with lung, gynecologic, and genitourinary tumors have chronic anemia.[7] A recent observational study of more than 15,000 cancer patients determined that 39% of all patients were anemic at study enrollment, with a higher incidence of new-onset anemia among patients who subsequently started chemotherapy.[8] Use of chemotherapy before surgery for cancer has been shown to worsen preoperative anemia, which may offset the benefits of neoadjuvant chemotherapy.[9] Therefore, cancer patients who undergo surgical intervention need to be assessed for anemia not only during and after surgery, but also as a key component of the preoperative workup.

Allogeneic blood transfusion alone is an inadequate solution to the problem of perioperative anemia in cancer patients such as those described previously, because it is a finite resource associated with infectious and noninfectious risks. Blood-conservation measures such as preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), perioperative blood salvage, minimizing perioperative phlebotomy, avoiding unnecessary anticoagulation, and the use of appropriate hemostatic agents may reduce allogeneic blood transfusion rates. Recombinant human erythropoietin (epoetin alfa) is indicated for the treatment of anemic patients who are scheduled to undergo elective, noncardiac, nonvascular surgery. Emerging techniques such as electrosurgical dissection and other minimally invasive surgical procedures may also reduce the need for allogeneic blood transfusion. The purpose of this review is to summarize published evidence of the consequences of anemia and blood transfusion, the effects of blood storage, the infectious and noninfectious risks of blood transfusion, and the role of blood-conservation strategies for cancer patients who undergo surgery.

CONSEQUENCES OF ANEMIA

Perhaps the most intuitive clinical consequence of anemia in surgical oncology is the need for perioperative blood transfusion. Clinical studies have confirmed the association between anemia and an increased risk of blood transfusion in surgical oncology.[1,3,10,11] Anemia may also be associated with increased postoperative morbidity and mortality, based on a meta-analysis of oncology studies that included patients who underwent surgery for cancer.[12] Results from recent studies in patients undergoing surgery for head and neck cancer, cervical cancer, uterine cancer, and non-small-cell lung cancer supported this conclusion by demonstrating that anemia is an independent prognostic factor for decreased locoregional control, disease-free survival, and overall survival.[13–18] Reviews of the available evidence have demonstrated a strong relationship between anemia and decreased quality of life in patients with cancer,[19,20] but clinical studies of this association typically have focused on chemotherapy-associated anemia, not anemia in patients with cancer who underwent surgery. Additional study would be needed to determine whether the association between anemia and postoperative morbidity, mortality, and quality of life exists in patients who are undergoing cancer-related surgery.

CONSEQUENCES OF BLOOD TRANSFUSION

Outcomes of Blood Transfusion

Despite evidence that anemia is associated with worsened outcomes, correction of anemia with blood transfusion does not appear to improve outcomes either. Withholding blood transfusions perioperatively in asymptomatic patients without cardiac disease with low-normal hemoglobin (Hb) levels, or even mild-to-moderate anemia, may be well tolerated. A randomized, controlled study of lung resection for non-small-cell lung carcinoma reported no improvement in morbidity and mortality when patients were transfused to maintain Hb > 10 g/dL compared with patients transfused to maintain Hb between 8.5 and 10 g/dL (Table 1).[21] These findings are consistent with similar randomized, controlled studies of critically ill anemic patients,[22] or patients undergoing surgery for hip fracture[23] or major vascular reconstruction,[24] in which more restrictive transfusion strategies did not worsen outcomes. The lowest "safe" Hb before blood transfusion remains an area of active research and lively debate.

TABLE 1. *Complications, mortality, and hospital stay among patients undergoing lung resection for carcinoma; use of a more aggressive blood transfusion strategy did not improve outcomes (Reprinted from Ref. 21, with permission from Elsevier BV)*

	Transfusion to Hb 8.5–10.0 g/dL (n = 49)	Transfusion to >10.0 g/dL (n = 149)	P value
Complications	13 (26.5%)	39 (26.2%)	.942
Atelectasis	3 (6.1%)	6 (4.0%)	.535
Chest infection	2 (4.1%)	9 (6.0%)	.61
Sputum retention	5 (10.2%)	12 (8.5%)	.853
Acute respiratory distress syndrome (ARDS)	0	3 (2.0%)	.319
Atrial fibrillation	4 (8.2%)	12 (8.0%)	.971
Bronchopleural fistula	0	1 (0.7%)	.567
Transfer to intensive care unit (ICU)	5 (10.2%)	7 (4.7%)	.158
Reoperation	2 (4.1%)	5 (3.4%)	.81
Deaths	1	3	.986
Hospital stay (days)	8.7 ± 2.6	9.1 ± 3.8	.49

Infectious Risks of Blood Transfusions

While allogeneic blood transfusion remains associated with a risk of disease transmission, the use of extensive testing and donor screening has resulted in a blood supply that is safer now than at any time in the past.[25] In developed countries, contamination of allogeneic red blood cells with parasitic infections is rare,[26] and the risk of viral disease transmission has become so small that mathematical models are used to assess it.[27–29] For example, the risk of HIV transmission in North America decreased from about 1:70,000 units of blood transfused in 1986 to between 1:1.8 million and 1:7.8 million units transfused in 2001–2005, due primarily to the use of nucleic acid technology (NAT) screening.[25,30,31] Similarly, the use of NAT has reduced the risk of hepatitis C to between 1:1.6 million and 1:3.0 million units transfused. The risk of transmission of hepatitis B, for which no NAT testing is available, is estimated to be 1:220,000 units transfused.

Although testing has been effective in reducing transfusion-related viral transmission, blood donations occurring after infection but prior to seroconversion remain a potential source of virus transmission. Additionally, the risk of virus transmission is highly dependent on socioeconomic factors, and developing countries have a much greater risk than developed countries of virus transmission in blood products.[32] Despite recent improvements in blood screening in developing areas,[33] many blood products that have been approved for transfusion in these areas may still be contaminated by viruses.[34]

Despite measurable progress, new threats continue to emerge. For example, transmission of variant Creutzfeldt–Jakob disease through blood transfusion has been reported.[35–38] After screening for West Nile virus began in the United States in June 2003, 163 units from a total of 1,100,000 units, or 1:6,748, tested positive in a 2-month period,[39] and more than 1,400 potentially infectious blood donations with West Nile virus were identified and removed by a national screening program between 2003 and 2005.[40]

Improved screening of the blood supply and exclusion of blood donors with risk factors for infections has reduced the risk of transfusion-transmitted viral infections in developed countries.[25] Consequently, the risk of bacterial contamination of blood products and posttransfusion sepsis now outweighs the risk of viral infection in these countries,[41] with a reported incidence between 1:28,000 and 1:143,000 for bacterial contamination.[30] Additionally, increased vigilance and rejecting potential blood donors at increased risk of viral infections has resulted in reduced blood supply, a limited margin between supply and demand, and increased cost.[42,43] The resulting blood shortages have been shown to lead to cancellation of elective surgery.[44,45] This has prompted numerous conservation measures and a search for alternative strategies that will help to manage this finite resource.

Noninfectious Risks of Blood Transfusions

As the risks of infectious complications have decreased, attention has shifted to more common and clinically important noninfectious risks (Table 2), such as human errors, hemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated graft-versus-host disease (GVHD), and transfusion-related immune modulation (TRIM).[46] The consequences of these complications can be severe. As noted in the sections below, most of these complications occur with <1% of all units of blood transfused. However, many cancer patients receive multiple units of blood perioperatively,[47] so the

TABLE 2. *Noninfectious complications of blood transfusion*

Complication	Approximate frequency (per units of blood transfused)
Human error (mismatched blood)	1:12,000 to 1:19,000[50] (some reports > 1:1,000[51,52])
Delayed hemolytic reaction	1:2,000 to 1:9,000[30,54,55]
Febrile nonhemolytic reaction	1:500[30]
Transfusion-related acute lung injury (TRALI)	1:1,120 to 1:7,000[30,54,55]
Graft-vs-host disease (GVHD)	1:1,000,000[54]

cumulative risk of noninfectious complications per patient is likely to be greater than is suggested by reported rates per transfusion.

Human Error and Acute Hemolytic Reactions

In the Serious Hazards of Transfusions (SHOT) study, systemic surveillance at >90% of hospitals in the United Kingdom found that 64–70% of reported events were attributable to errors in the transfusion process, including administration of ABO-incompatible blood for nearly 1 in 8 reported events.[46,48] The same group reported that 52% of deaths and major events after blood transfusion were caused by clerical error.[49] A review of the scope of the problem in the United States concluded that approximately 1:12,000 to 1:19,000 units of blood transfused are associated with ABO errors.[50] Reports from other developed countries have suggested the risk of human error at some point in the whole-blood transfusion chain may be 1:1000,[51] with a rate as high as 1:400 in one study.[52] Human errors remain common despite educational efforts, regulations, and technological advances to improve the accuracy of blood transfusion.[53]

Human errors are responsible for more than half of all transfusion-related fatalities.[50,54] Mismatched blood may lead to an acute hemolytic reaction, which is characterized by fever, chills, pain, nausea, vomiting, hypotension, tachycardia, renal failure, and disseminated intravascular coagulation, with death in up to 40% of cases.[54]

Delayed Hemolytic Reaction

The reported incidence of delayed hemolytic reactions is between 1:2,000 and 1:9,000 units of blood transfused in developed countries.[30,54,55] The true incidence may be higher because milder cases are either undiagnosed or unreported.[30] Signs and symptoms of delayed hemolytic reactions occur 3 days to 2 weeks after transfusion and include failure to maintain Hb levels, fever, chills, dyspnea, and jaundice. These delayed reactions are characterized by extravascular hemolysis caused by antibodies directed at red blood cell antigens.[55] In general, delayed hemolytic reactions are less severe than acute hemolytic responses, but fatalities have been reported.[54]

Febrile Nonhemolytic Reaction

A common reaction to blood transfusion involves temporary elevation of body temperature by ≥1°C within 1–2 hours after the transfusion. It is estimated that febrile nonhemolytic reactions occur with an incidence of approximately 1:500 units transfused, but rates as high as 1–2% have been reported.[30] Although febrile nonhemolytic reactions are not life-threatening, they may be a cause of concern and confusion in perioperative cancer patients because the fever may be misinterpreted as a sign of infection resulting either from surgery or from immunosuppression.

Transfusion-Related Acute Lung Injury

The term TRALI was coined in 1983[56] and the first fatality from TRALI was reported to the FDA in 1992.[57] The reported incidence of TRALI[30,54,58] has ranged widely from 1:1,120 to 1:70,000. This range may reflect changes in blood storage; the greatest risk was reported in the 1980s, when red blood cells were suspended in substantially more plasma, whereas the lower-risk estimates were obtained in 2000–2001 with the standardized use of additive storage solutions for red blood cells.[30] The mechanism of TRALI is not completely understood, but it appears to involve localization of antibody-coated leukocytes to pulmonary vasculature resulting in increased permeability and edema.[59] Presenting signs and symptoms of TRALI include dyspnea, hypotension, fever, and bilateral pulmonary infiltrates without evidence of cardiac compromise or fluid overload. Symptoms begin during or shortly after transfusion, and TRALI develops fully within 1–6 hours. TRALI is fatal in 5–10% of cases,[54] and it may be responsible for more serious adverse events and fatalities than are reported because it is often misdiagnosed.[60] When TRALI occurs, oxygen therapy should be initiated immediately, the transfusion should be stopped, and the remaining blood product should be returned to the blood center for testing. Prompt identification and treatment of TRALI is important to minimize the risk of fatality and optimize long-term prognosis.[56,57]

Graft-Versus-Host Disease

Transfusion-related GVHD is rare (approximately 1:1 million units transfused), but lethal in about 90% of cases when it occurs.[54] It is caused by proliferation of donor T-lymphocytes in susceptible patients.[61] T-lymphocytes in the transfused blood recognize host human leukocyte antigens (HLA) as foreign and mount an immune response against the host (i.e., the transfusion recipient). Clinical evidence of GVHD such as fever, cutaneous eruption, diarrhea, and liver test abnormalities appears within 1 week, with death occurring within 3–4 weeks of the transfusion for the most serious cases.

Transfusion-Related Immune Modulation and Cancer Recurrence

Transfusion-related immune modulation was first noted more than 3 decades ago by Opelz and colleagues, who reported that subjects who had received more than 10 allogeneic blood transfusions prior to receiving a cadaver kidney transplant had better allograft survival than subjects who had never received an allogeneic blood transfusion.[62] TRIM has also been proposed as a reason for the higher rates of cancer recurrence that have been observed in some studies.[47] The presence of leukocytes has been implicated in these responses, and universal leukoreduction has been proposed and implemented in many institutions; however, a meta-analysis of 14 randomized clinical trials failed to show an association between leukoreduced transfused red cells and long- or short-term mortality.[63] In another report[64] of two meta-analyses, a statistically and clinically significant reduction in the risk of infection was observed among transfused patients who received leukoreduced blood compared with those who received standard blood transfusions, but the overall risk reduction (i.e., including patients who did not receive a transfusion) was not significant.

The key clinical implication of TRIM in surgical oncology is the potential for increased cancer recurrence. Numerous clinical studies have reported that surgical oncology patients who receive blood transfusions may have greater risk of postoperative complications, decreased locoregional control, lower disease-free survival, and lower overall survival.[47,65,66] More than 150 clinical studies have been published on this topic.[66] Many studies have reported an association between perioperative transfusions and either cancer recurrence or postoperative bacterial infection, but a causal relationship for cancer recurrence has not been established because of the heterogeneity of the studies.[47,66]

Several recent observational studies have provided support for an independent effect of blood transfusion and cancer recurrence.[67–73] Some of these studies reported a positive association only among subgroups of patients according to tumor stage[67–70] or when the patient received the blood transfusion relative to surgery.[71] Unfortunately, it is difficult to perform a controlled clinical study that will confirm an independent effect of allogeneic blood transfusion on cancer recurrence. For ethical and logistic reasons, surgical oncology patients cannot be assigned to a "no-transfusion" group. Therefore, PAD or allogeneic transfusion alone are commonly used as control groups in clinical trials.[74–76] Busch et al. concluded that PAD before surgery for colorectal cancer reduced the use of allogeneic blood transfusion, but did not improve recurrence rates and disease-free survival.[74,75] However, the use of blood transfusion—either allogeneic or autologous—was associated with increased cancer recurrence. Heiss et al. also found no significant difference in disease-free survival after surgery in patients with colorectal cancer who donated blood preoperatively compared with patients who did not.[76] In a multivariate analysis, the investigators reported that allogeneic blood transfusion was associated with a greater than 6-fold increase in the relative risk of tumor recurrence in both treatment groups. Another controlled study by van de Watering et al. determined that patients with colorectal cancer had comparable survival and recurrence rates if they were transfused with leukocyte-depleted allogeneic blood or with packed red blood cells with leukocytes.[77]

One possible interpretation of the available evidence is that the need for blood transfusions is simply a marker for sicker patients who are more likely to have worse long-term outcomes, rather than a direct effect of blood transfusion.[66] Regardless of whether the association is independent of or dependent on other factors, the use of allogeneic blood in surgical oncology has been repeatedly associated with poor postoperative outcomes. Patients who require neither autologous nor allogeneic blood transfusions may have the lowest risk of morbidity and mortality.

Effects of Blood Storage

Current regulations in the United States allow donated blood to be stored up to 42 days before transfusion.[78] During blood shortages, up to 38% of stored blood is within 3 days of being out of date.[78] Morphologic and biochemical changes occur during

storage that may limit the effectiveness of allogeneic blood by altering the deformability, survival, and oxygen-carrying capacity of red cells after transfusion.[78] Additionally, inflammatory cytokines and other bioactive molecules are generated during storage and may contribute to the adverse effects associated with allogeneic blood transfusion.[78,79] Several retrospective clinical studies have found an association between the age of allogeneic blood and the incidence of infection or multiple organ failure syndrome.[80,81] However, a small randomized clinical study of 57 critically ill and cardiac surgery patients demonstrated that the use of blood stored for a median of 4 days did not improve morbidity or mortality compared with blood stored for a median of 19 days.[82] Thus, the available evidence does not support the theory that recently donated blood confers any benefit over blood stored nearly five times longer. However, comparisons of short-term (i.e., < 1 week) and long-term storage of blood (i.e., 5–6 weeks) before perioperative transfusion may be necessary before firm conclusions can be made regarding the effects of blood storage on transfusion outcomes.

BLOOD-CONSERVATION STRATEGIES

Numerous blood-conservation strategies have been recommended for patients who undergo surgery to reduce reliance on blood transfusions. Strategies described in the following sections include PAD, ANH, perioperative blood salvage, perioperative use of epoetin alfa, emerging technologies such as artificial oxygen carriers and electrosurgical dissection, and other blood-conserving approaches such as minimizing perioperative phlebotomy, avoiding unnecessary anticoagulation, and using appropriate hemostatic agents. These strategies may be warranted universally in surgical oncology because of the high prevalence of anemia in cancer patients and the apparent link between blood transfusion and negative outcomes, as described previously. Indeed, all surgical patients are likely to benefit from some degree of blood conservation, even if not all of the available strategies are used in all patients.

Guidelines for Detection and Management of Anemia

Clinical guidelines for the detection and management of anemia may be valuable tools for the identification of patients who could benefit from blood conservation. The currently available clinical guidelines focus on anemia of chronic disease and chemotherapy-related anemia.[83–85] Until similar guidelines become available for patients undergoing surgery for cancer, application of some of the existing guidelines to surgical patients may help to conserve blood in this setting as well.

Protocols and algorithms for the identification of patients at risk of perioperative anemia also may be helpful to guide selection of blood-conservation strategies. A transfusion-prediction risk-assessment model in head and neck cancer surgery was developed based on data from one institution[86] and validated at another institution.[1] Despite an overall transfusion rate of 12% at one institution and 25% at the other, surgical complexity (flap vs no flap), tumor stage (T3/T4 vs non-T3/T4), and preoperative Hb (low vs normal–high) successfully predicted high-, intermediate-, and low-risk of blood transfusion at both institutions. Based on their findings, the authors recommended using these patient-specific factors to guide decisions about blood conservation in head and neck cancer surgery.

Preoperative Autologous Blood Donation

The technique of PAD was developed in the 1980s in response to the serious risk of HIV transmission from allogeneic transfusions. In 1980, PAD represented only 0.25% of all blood donations in the United States; it peaked at 8.5% in 1992 and declined slowly thereafter, reaching 4.0% in 2001.[87] Patients can donate a unit of blood up to twice weekly until 3 days before surgery, but in practice, patients undergoing PAD usually donate a single unit per week.

In theory, PAD offers advantages over allogeneic transfusions because it prevents the transmission of disease, supplements the total blood supply, and prevents some of the adverse reactions associated with allogeneic transfusions. However, PAD is not without disadvantages and risks. Preoperatively, visits for PAD can be inconvenient, and severe complications of blood donation are 12 times more common for PAD than for allogeneic donation, possibly due to preexisting serious conditions in autologous donors.[88] Autologous blood may be stored for long periods before transfusion, and PAD is more expensive than allogeneic donation because of patient-specific collection and storage procedures.[89] Compensatory erythropoiesis after PAD replaces approximately only 60% of the red blood cells donated; thus, patients are more likely to be anemic preoperatively.[87] Physicians may administer autologous transfusions more liberally because of the perceived lower risks, leading to volume

overload.[90] Conversely, it is difficult to predict how much blood a patient will need, and units that are not transfused are discarded rather than released into the general blood supply.[91,92]

As described in the previous section, the major drawback of PAD is that it is associated with a decrease in disease-free survival among cancer patients that is comparable to the risk associated with allogeneic transfusion. Both forms of blood transfusion are associated with approximately a 2-fold increase in cancer recurrence,[74] the risk of which may far outweigh the putative benefits of PAD for infectious disease transmission. Additionally, PAD reduces but does not eliminate the need for allogeneic blood transfusion; for example, between 1:4 and 1:3 patients with colorectal cancer who underwent PAD in controlled trials still required allogeneic transfusions perioperatively.[74,76] Finally, reinfusion of blood that is collected by PAD does not eliminate the risk of clerical error or blood contamination from bacterial infection.

Acute Normovolemic Hemodilution

If substantial perioperative blood loss is anticipated, ANH may reduce loss of cellular components of blood and reduce the need for allogeneic transfusion.[93] ANH is performed around the time of induction of anesthesia, by removing whole blood from the patient while maintaining normal blood volume with simultaneous infusion of a crystalloid and/or colloid solution. The blood is stored during surgery and returned to the patient when needed, either for a major bleeding episode during surgery or when surgery is complete. ANH is thought to reduce red cell loss during surgery because fewer red cells are lost in diluted blood. Other advantages include its low cost, patient convenience, and the low risk of administrative error because the blood remains with the patient.

It is simple in concept, but the efficacy of ANH in reducing risk of allogeneic blood transfusion in surgical oncology has not been established. In a randomized study of 79 patients who underwent prostatectomy, ANH and PAD reduced the need for allogeneic transfusion comparably, but ANH was less costly than PAD.[10] However, the study did not include a group that received only allogeneic transfusion. A meta-analysis of 42 randomized studies concluded that ANH had no significant effect on transfusion risk when compared with either other blood-conservation methods or allogeneic transfusion.[94]

Perioperative Blood Salvage

Collection and reinfusion of autologous red blood cells (perioperative blood salvage) may reduce the need for allogeneic transfusion. The process is generally considered to be safe, but several clinical issues remain. Shed blood contains higher concentrations of inflammatory mediators—such as IL-6, IL-8, and TNF-α—than circulating blood.[95,96] Tumor cells also may be present in shed blood, so blood salvage historically was considered to be contraindicated during certain oncology surgeries.[97] More recently, clinical studies have demonstrated that filtration or irradiation of shed blood may remove tumor cells. A pilot study of leukocyte filtration in 16 lung cancer patients who were treated with perioperative blood salvage reported that tumor cells were present in salvaged blood of 9 of 16 patients before filtration, but in none of the blood after filtration.[98] Another study evaluated 62 patients who were treated with cell salvage and leukocyte filtration during prostatectomy, compared with a historical group of 101 patients who underwent PAD.[99] The cell-salvage group had higher hematocrit values and required fewer allogeneic blood transfusions perioperatively, yet rates of progression-free survival were comparable between groups. Another study evaluated 20 consecutive patients who underwent either pancreaticoduodenectomy or major hepatectomy for the presence of malignant cells from autotransfusion filtered blood following resection.[100] This prospective study evaluated all intraoperative blood loss that was designated for waste from opening to closure and was collected, filtered, and prepared for autotransfusion. The preparation was then evaluated by flow cytometric and immunohistochemical methods to see if any malignant cells could be autotransfused back into the patient. Flow cytometry did not demonstrate the presence of any cytokeratin-positive carcinoma cells in filtered blood, and the authors concluded that intraoperative autotransfusion for major hepatectomy in metastatic colorectal cancer and pancreatectomy for adenocarcinoma is safe. Finally, a group of researchers reported that in more than 700 surgical oncology patients, they were able to eradicate tumor cells in salvaged blood via high-dose irradiation of the blood prior to reinfusion.[101] Therefore, leukocyte filtration or irradiation of salvaged blood may mitigate concerns about the potential for reinfusion of tumor cells.

Although perioperative salvage and reinfusion of shed blood is simple and appears to be safe in surgical oncology, studies from other surgical procedures

have failed to demonstrate a consistent reduction in transfusion requirements.[102] Furthermore, perioperative blood salvage may not be cost effective unless at least 2 units of blood are recovered and reinfused.[102,103]

Preoperative Epoetin alfa

Epoetin alfa is indicated for the treatment of anemic (pretreatment Hb of >10 to ≤13 g/dL) patients who are scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[104] In randomized, double-blind clinical trials, epoetin alfa increased Hb and/or decreased perioperative blood transfusion requirements in patients who underwent surgery for head and neck cancer[105] and gastrointestinal cancer.[106] In the comparative study described previously that compared ANH and PAD in patients with prostate cancer, a third arm received a combination of epoetin alfa and ANH perioperatively.[10] Epoetin alfa plus ANH resulted in higher hematocrit throughout hospitalization compared with ANH alone or PAD alone. As per product labeling, the recommended dose of epoetin alfa in elective surgery is 300 IU subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery. An alternative dose schedule is 600 U/kg subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[104] All patients should receive adequate iron supplementation throughout the course of epoetin alfa therapy.

Overall, adverse events were reported with comparable frequency between the epoetin alfa group and the placebo group in clinical studies of surgical patients.[104] However, recent clinical trial data have raised potential questions about the safety of erythropoiesis-stimulating agents in patients with anemia associated with chronic renal failure and cancer. Increased mortality, tumor progression, serious cardiovascular events, and thromboembolic events were observed in clinical studies of those populations when erythropoiesis-stimulating agents were dosed to Hb levels higher than those indicated in the product labeling. An increased incidence of deep-vein thrombosis was also observed in patients who received erythropoiesis-stimulating agents preoperatively and did not receive prophylactic anticoagulants. These results have led to recent (March 2007) revisions with updated safety information to product labeling for erythropoiesis-stimulating agents.[104,107,108]

Nutritional Supplementation

Perioperative deficiencies of iron and vitamin B_{12} have been reported in cancer patients.[109–111] Functional iron-deficiency may also occur in cancer patients, even when iron levels appear normal or elevated, because the iron requirements of increased erythropoiesis may exceed the existing iron stores.[112] Therefore, supplementation of vitamin B_{12}, folate, and iron should be considered as part of routine perioperative care of cancer patients, regardless of the other blood-conservation strategies that are used. Systematic reviews of the available evidence suggest that intravenous administration of iron is preferable to oral administration in cancer patients, particularly when erythropoietic therapy is administered.[113]

Emerging Technologies

The limited supply and relatively short shelf life of donated blood and the risks associated with allogeneic blood transfusions have spurred the research and development of artificial oxygen carriers as red cell substitutes. Two major types of oxygen carriers are being evaluated for clinical use: bioartificial oxygen carriers that are based on Hb and synthetic oxygen carriers that are commonly based on perfluorocarbons.[114] Neither type has been approved for use in the United States.

Bloodless Medicine

New approaches to medical care, collectively termed "bloodless medicine," have been developed to reduce blood loss and limit the need for allogeneic blood transfusions. These approaches include the use of novel surgical instruments that minimize bleeding and minimally invasive surgical procedures.[115,116]

One of these techniques, electrosurgical dissection, was performed for major surgical procedures in 250 head and neck cancer patients at one institution; a total of 66 units of packed red blood cells were given to 30 (12%) patients.[117] The authors concluded this rate was lower than expected for patients who undergo standard operative intervention, based on a previous study that reported a transfusion rate of 58% in the control group.

Meticulous surgical techniques, minimization of perioperative phlebotomy, and avoidance of anticoagulation in all surgical patients may also reduce unnecessary blood loss, regardless of transfusion risk.[118] Prohemostatic therapy such as desmopressin,

recombinant activated factor VII, antifibrinolytics, vitamin K, fibrin sealants, and aprotinin may be effective in reducing perioperative blood loss and reducing the need for allogeneic transfusions.[119] An evidence-based review of aprotinin in orthopedic surgery concluded that it was efficacious for blood conservation in general; however, its use could not be recommended in cancer patients because of conflicting evidence in this population.[120] Furthermore, a review of >500 clinical publications concluded that aprotinin should be withdrawn from human use because of serious concerns such as thrombosis, renal dysfunction, and hypersensitivity reactions in cardiac patients.[121]

CONCLUSIONS

Although the prevalence of anemia in surgical oncology may vary widely, acute blood loss during oncologic surgery often is compounded by the existence of several cancer-related factors such as anemia of chronic disease, poor nutrition, or chemotherapy. Several studies have reported that anemia worsens morbidity and mortality in surgical oncology patients, and the use of blood transfusion may exacerbate—not ameliorate—these sequelae. Blood-conservation strategies such as PAD, ANH, perioperative blood salvage, and minimally invasive surgical techniques can reduce dependence on blood transfusion, and epoetin alfa can be used in the treatment of anemic patients who are scheduled to undergo elective, noncardiac, nonvascular surgery. Randomized clinical trials have reported these strategies do not worsen clinical outcomes relative to allogeneic blood transfusion. However, there is no conclusive evidence of a beneficial effect of a particular blood-conservation strategy in cancer patients who undergo surgery, and the optimal blood management strategy remains to be defined by additional clinical studies. Until that evidence becomes available, the clinical utility of blood conservation should be assessed for each patient individually as a component of preoperative planning in surgical oncology.

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