Blood Transfusions, Thrombosis, and Mortality in Hospitalized Patients With Cancer

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Background: Anemia is frequent in patients with cancer, but there are concerns regarding treatment with erythropoiesis-stimulating agents. Blood transfusions are commonly used as an alternative, but with little data regarding outcomes.

Methods: In a retrospective cohort study, we investigated the associations between transfusions and venous thromboembolism, arterial thromboembolism, and mortality in hospitalized patients with cancer using the discharge database of the University HealthSystem Consortium, which included 504,208 hospitalizations of patients with cancer between 1995 and 2003 at 60 US medical centers.

Results: Of the patients included, 70,542 (14.0%) received at least 1 red blood cell (RBC) transfusion and 15,237 (3.0%) received at least 1 platelet transfusion. Of patients receiving RBC transfusions, 7.2% developed venous thromboembolism and 5.2% developed arterial thromboembolism, and this was significantly greater than the rates of 3.8% and 3.1%, respectively, for the remaining study population (P < .001). In multivariate analysis, RBC transfusion (odds ratio [OR], 1.60; 95% confidence interval [CI], 1.53-1.67) and platelet transfusion (1.20; 1.11-1.29) were independently associated with an increased risk of venous thromboembolism. Both RBC transfusion (OR, 1.53; 95% CI, 1.46-1.61) and platelet transfusion (1.55; 1.40-1.71) were also associated with arterial thromboembolism (P < .001 for each). Transfusions were also associated with an increased risk of in-hospital mortality (RBCs: OR, 1.34; 95% CI, 1.29-1.38; platelets: 2.40; 2.27-2.52; P < .001).

Conclusions: Both RBC and platelet transfusions are associated with increased risks of venous and arterial thrombotic events and mortality in hospitalized patients with cancer. Further investigation is necessary to determine whether this relationship is causal.

Arch Intern Med. 2008;168(21):2377-2381

Aneemia is observed in 30% to 90% of patients with cancer. It is exacerbated by blood loss during surgery, myelosuppression related to chemotherapy, and radiotherapy. Anemia can result in symptoms such as fatigue and angina in patients with coronary artery disease, and it is associated with a reduction in quality of life. Erythropoiesis-stimulating agents (ESAs) are often used to treat anemia in patients with cancer. However, recent studies suggest an increased risk of thromboembolic complications and decreased survival with the use of ESAs in cancer. This has led to a Food and Drug Administration advisory restricting their use. Red blood cell (RBC) transfusions are often used as an alternative treatment for anemia in patients with cancer and are recommended as therapeutic options by the American Society of Clinical Oncology/American Society of Hematology guidelines. However, there are no randomized controlled trials, to our knowledge, demonstrating improved outcomes or quality of life in patients with cancer receiving transfusions, and the safety profile of RBC transfusion in patients with cancer has not been studied as rigorously as that of ESAs.

Studies attempting to assess the benefit of transfusions in noncancer settings have reported conflicting findings. A randomized study found no benefits of transfusion in critically ill patients to maintain a hemoglobin level of 10 g/dL (to convert to grams per liter, multiply by 10.0) compared with restricting transfusion to patients with a hemoglobin level of 7 g/dL or lower. Indeed, patients with the more conservative transfusion indication had superior survival overall. A recent pooled analysis of clinical trials showed that patients with acute coronary syndromes receiving transfusion had a higher rate of myocardial infarction and death. In contrast, blood...
transfusion in elderly patients with myocardial infarction has been associated with a lower 30-day mortality rate in more severely anemic patients, although mortality was higher in transfused patients who were mildly anemic. Blood transfusions have also been linked to an increased long-term risk of cancer. Platelet transfusions have been linked to deep venous thrombosis in critically ill patients and to adverse outcomes, including stroke, after coronary artery bypass surgery. There is a scarcity of similar data in patients with cancer, although perioperative transfusions of RBCs and fresh frozen plasma were reported to be associated with venous thromboembolism (VTE) in a small cohort of patients undergoing gynecologic surgery for cancer. Similar preliminary findings have recently been reported in other surgical settings, suggesting an association between perioperative transfusions and thrombosis and even survival.

The objective of this study is to determine the relationship between blood transfusion and outcomes in hospitalized patients with cancer. We analyzed data from hospital discharge summaries of all patients with cancer admitted to 60 US academic medical centers between 1995 and 2003 to investigate the associations between transfusions and thromboembolic events and in-hospital mortality.

### METHODS

All discharge summaries of adult patients with cancer admitted between 1993 and 2003 to 1 of 60 academic medical centers in the United States were reviewed using the discharge database of the University HealthSystem Consortium. To avoid centers not reporting or inconsistently reporting transfusion data, only hospitals reporting packed RBC transfusions in at least 2% of admissions and platelet transfusions in at least 0.1% of admissions during every year of the study were included in this analysis. These criteria correspond to the lowest quartile of all University HealthSystem Consortium institutions. Patients were identified using International Classification of Diseases, Ninth Revision, Clinical Modification, codes that contained at least 1 diagnosis of malignant disease (codes 140-208). Patients who received transfusions were identified using procedure codes for packed RBCs (code 99.04), platelets (code 99.05), and autologous whole blood (code 99.02). Patients with VTE were identified using codes for venous thrombosis (codes 451, 452, and 453) and pulmonary embolism (codes 415.1-415.19). Patients with arterial thromboembolism (ATE) were identified using codes for arterial embolism (codes 444), acute cerebrovascular disease (codes 433-434 and 436), and acute coronary artery disease (codes 410 and 411.1-411.8). Patients undergoing active therapy were identified using codes for chemotherapy (codes 99.25, V58.1, and V67.2), high-dose interleukin 2 (code 00.15), biological therapy (code 99.28), adverse events from chemotherapy (codes E930.7 and E933.1), and neutropenia (code 288.0). Selected surgical oncologic procedures included mastectomy or lumpectomy (codes 85.21-85.23, 85.34, 85.36, and 85.4), unilateral or bilateral radical cervical lymph node dissection (code 40.4), partial or total pancreatectomy (codes 52.5-52.7), neurosurgery (codes 01.1-01.39 and 01.5-01.39), and spinal surgery (codes 03.0, 03.09, 03.3, 03.32, 03.39, and 03.4). Patients with catheters were identified using codes 38.93, 86.06, and 86.07. Comorbidities and risk factors included infection (codes 001-139.8, 480-486, and 996.62), pulmonary disease (codes 487-519), hypertension (codes 401), renal disease (codes 580-593), diabetes mellitus (codes 230), congestive heart failure (codes 428), hepatic disease (codes 570-576), anemia (codes 280-285), and obesity (code 278.0).

### RESULTS

The study population comprised 504,208 patients with cancer admitted between 1995 and 2003 at 60 medical centers (Table 1). More than one-third of the patients were 65 years or older. More than two-thirds of the population was white, with blacks representing 12.3% and Hispanics 4.6%. Venous thromboembolism occurred in 21,040 patients (4.2%), including 17,613 (3.5%) with deep venous thrombosis and 5547 (1.1%) with pulmonary embolism; ATE events occurred in 16,651 patients (3.3%).

### TRANSFUSIONS

Of the study population, 74,051 patients (14.7%) received either packed RBC or platelet transfusions. Of these, 70,542 (14.0%) received at least 1 RBC transfusion and 15,237 (3.0%) received at least 1 platelet transfusion (Table 1). Only 3509 patients (0.7%) received solely platelet and no RBC transfusions and 11,728 (2.3%) received both platelet and RBC transfusions. An additional 2939 patients (0.6%) received autologous whole blood or RBC transfusions. For further analysis, patients receiving platelet and RBC transfusions were included in the platelet transfusion category, whereas patients receiving only RBC transfusions were included in the RBC transfusion category.

Venous thromboembolism occurred in 4234 of 58,814 patients (7.2%) receiving RBC transfusions only, 770 of
11,728 (6.6%) receiving both RBC and platelet transfusions, and 223 of 3509 (6.4%) receiving platelet transfusions only. These rates were substantially higher than the VTE rate of 3.7% in hospitalized patients with cancer not receiving transfusions (P < .001). Arterial thromboembolism occurred in 3034 patients (5.2%) receiving RBC transfusions only, 524 (4.5%) receiving both RBC and platelet transfusions, and 108 (3.1%) receiving platelet transfusions only. Again, these rates were significantly higher than the ATE rate of 3.0% in hospitalized patients with cancer not receiving transfusions (P < .001). Rates of VTE (0.9%) and ATE (0.6%) were low in the few patients (N = 2939) receiving whole blood autologous transfusions.

### MULTIVARIATE ANALYSIS

In a multivariate logistic regression analysis, RBC transfusions (odds ratio [OR], 1.60; 95% confidence interval [CI], 1.53-1.67; P < .001) and platelet transfusions (OR, 1.53; 1.46-1.61; P < .001) were independently associated with VTE. Other variables significantly associated with VTE included age 65 years and older, female sex, use of chemotherapy, primary site of cancer, use of venous catheters, and the presence of comorbidities (including anemia, infection, and renal and lung disease) (Table 2). Both RBC transfusions (OR, 1.53; 95% CI, 1.46-1.61; P < .001) and platelet transfusions (OR, 1.55; 1.40-1.71; P < .001) were also independently associated with ATE in a separate multivariate analysis. Other variables associated with ATE included age 65 years and older, male sex, primary site of cancer (including prostate, colon, lung, gastrointestinal, lymphoma, and leukemia), use of venous catheters, and the presence of comorbidities (including congestive heart failure, hypertension, diabetes mellitus, pulmonary and renal disease, and tobacco abuse).

### IN-HOSPITAL MORTALITY

Data regarding in-hospital mortality were available for 503,185 patients (99.8% of the study population). Death during hospitalization occurred in 33,924 patients (6.7%). In-hospital mortality was higher in patients receiving RBC transfusions (11.9%) and platelet transfusions (23.1%). In-hospital mortality was also significantly higher in patients with VTE (16.7%) and ATE (19.3%). In a multivariate analysis, RBC transfusions (OR, 1.34; 95% CI, 1.29-1.38; P < .001) and platelet transfusions (2.40; 2.27-2.52; P < .001) continued to be independently associated with an increased risk of in-hospital mortality after adjusting for other known risk factors for mortality. Other variables significant in this analysis included older age, primary site of cancer, nonwhite race/ethnicity, VTE, ATE, and the presence of comorbidities.

### COMMENT

Using a large nationwide database of hospitalized patients with cancer, we found that 7.2% of patients receiving RBC transfusions had VTE and 5.2% had ATE, and...
these rates were significantly higher than the 3.8% and 3.1%, respectively, in the remaining study population. In multivariate analysis, use of RBC and platelet transfusions was significantly associated with VTE, ATE, and inhospital mortality after adjusting for other covariates.

A variety of possible mechanisms might explain the associations reported herein, if eventually proved to be causal. A major effect of transfusion is the delivery of large amounts of redox-active iron, which has been linked to cardiovascular disease because of increased iron-catalyzed free radical–mediated oxidative stress.18 Indeed, several variables associated with vascular events in this analysis, including age, race/ethnicity, and comorbidities, have been linked to increased body iron stores as well.19 Alternatively, RBC transfusions, by increasing the circulating RBC mass, may improve hemostasis, with one consequence being an increased risk of thrombosis.20 Stored RBCs are severely depleted in nitric oxide, which may lead to vasoconstriction and increase the risk of thrombosis due to vascular rheologic changes and increased platelet activation.21 Furthermore, nonleukoreduced RBCs and all platelet transfusions contain proinflammatory and prothrombotic soluble mediators, such as sCD40L, platelet microparticles, and activated platelets, which could contribute to the prothrombotic state in patients with cancer.22,23,24 Other risk factors for VTE reported herein, including age, site of cancer, the presence of comorbidities, and chemotherapy, are consistent with previous studies.22,23,24

All of the platelet transfusion recipients and many of the RBC transfusion recipients were likely thrombocytopenic to some degree, the platelet transfusion recipients severely so. This suggests that severe thrombocytopenia may not protect against VTE and ATE, a novel and somewhat counterintuitive finding. However, this is consistent with recent data suggesting that patients with hematologic malignant neoplasms, who are often myelosuppressed, have an elevated risk of VTE similar or even greater than that observed in patients with solid tumors.27 The role of platelets in the multifactorial etiology of cancer-associated thrombosis is, however, unclear.

Limitations of this analysis include its reliance on administrative coding. However, codes for VTE and comorbidities have been validated in previous studies and are considered to be accurate.28-31 The diagnostic criteria to identify VTE included superficial thrombophlebitis, but less than 1% of patients were in this category and, therefore, did not substantially affect the analysis. We controlled for underreporting of transfusion by excluding hospitals that did not report transfusions or that were in the lowest quartile of hospitals reporting transfusions. This data set does not allow us to identify patients concomitantly receiving ESAs as part of outpatient therapy, a potential confounding factor. Data regarding compliance with appropriate thromboprophylaxis were also unavailable. A major limitation of this analysis is the inability to determine the time of administration of transfusion in relation to the development of thromboembolic events or to identify patients admitted with VTE who subsequently required transfusions. To account for this, however, we excluded patients with a primary diagnosis of VTE or ATE from the multivariate analyses. Finally, it is possible that anemia is a surrogate for aggressive tumor biology, more intense chemotherapy, or “sicker” patients, although, in this analysis, transfusions continued to be associated with poor outcomes even after adjusting for type of cancer and comorbidities.

Controversy exists regarding the treatment of anemia in cancer with ESAs because of potential adverse effects, including thromboembolism and worsened survival. Data presented herein suggest caution in using transfusions as an alternative to ESAs because these may carry a similar risk of adverse thrombotic and survival outcomes. These findings suggest that rigorous studies evaluating the risks and benefits of blood transfusion in patients with cancer are necessary.

Accepted for Publication: June 2, 2008.
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Financial Disclosure: Dr Khorana has received consultant fees and honoraria from Sanofi-Aventis, Eisai, and Amgen; Dr Francis has received consultant fees and honoraria from Eisai, Boehringer-Ingerheim, Amgen, Pfizer, and Takeda; Dr Blumberg has received consultant fees and honoraria from Bayer, Baxter, Pall, and Gambro; and Dr Lyman has received honoraria and research funding from Amgen.

Funding/Support: This study was supported, in part, by grant K23 CA120587 from the National Cancer Institute (Dr Khorana) and by grants R21 HL086367 and R01 HL078603 from the National Heart, Lung, and Blood Institute (Drs Blumberg and Francis).

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