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Risk of thrombosis in cancer and the role of supportive care (transfusion, catheters, and growth factors)

Giancarlo Castaman*

Center for Bleeding Disorders, Department of Heart, Lung, and Vessels, Careggi University Hospital, Florence, Italy

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ABSTRACT

Thrombosis in cancer patients is a well-known, frequent complication which can adversely influence treatment outcome and mortality rate. Several cancer-related or patient-related factors may contribute in modulating the magnitude of the risk. Among the treatment-related factors, the use of blood transfusions, erythropoiesis stimulating agents and central venous catheters play a significant role in influencing the epidemiology of thromboembolism in cancer patients. Red cell transfusions may influence the risk of both arterial and venous thromboembolism (VTE), although the mechanisms of causal relationship have not clearly elucidated. A judicious use should be considered, especially for active bleeding with the risk of significant anemia and the presence of cardiovascular risk factors. The use of erythropoiesis stimulating agents carries a definite risk of thrombosis in cancer patients and there is still a debate on whether they can also influence cancer biology and thus clinical outcome. Their use should be carefully weighed considering the duration of chemotherapy courses and the possible short-term benefits of these agents. Catheter-related thrombosis may be present in about 1-5% of cancer patients but asymptomatic cases detected by close ultrasound monitoring may be by far higher. Tailored anti-thrombotic treatment should be undertaken according to the presence of risk of bleeding (e.g., thrombocytopenia). Thrombophylaxis should be considered in patients with a high-risk prothrombotic profile.

Introduction

Thrombosis, and in particular venous thrombosis (VTE), is a frequent complication of cancer, often influencing clinical follow-up and the course of the disease in a significant proportion of cases [1]. Furthermore VTE is an independent risk factor for mortality [2]. In outpatients on chemotherapy, mortality rates over a 75-day period have been reported to approach 9%, and VTE represented the second cause of death in this study population [3]. VTE may delay the specific treatment of tumor and requires often increased hospitalization with aggravation of healthcare costs. In addition, the requirement for anticoagulant treatment may further complicate the overall picture by adding the risk of bleeding complications.

Several risk factors for cancer-associated VTE have been identified. First of all, the risk is strongly dependent by the type of tumor, advanced stage and metastatic disease. In addition to the particular type of cancer, patient and treatment-related risk factors may add to strongly influence the risk of VTE (Table 1). The presence of one or more of these factors, permanently or transiently, modulates the risk of VTE during follow-up and should be carefully taken into account to evaluate the most appropriate prophylaxis or the type of specific treatment.

In this review we will focus in particular on VTE risk associated with transfusional treatment, use of growth factors and venous access devices.

Transfusional treatment

Anemia may frequently occurs in patients with cancer. In addition to patients with blood malignancies, frequently transfused, also patients with solid tumors may require supportive treatment, especially with packed red cells and more rarely with plasma or platelet concentrates as a result of bone marrow suppression by chemotherapy, radiation treatment, metastatic stage or because of inter-current bleeding.

Evidence coming from small studies have suggested that perioperative transfusions of red cells and fresh frozen plasma may be associated with increased risk of VTE in cohorts of patients undergoing surgery for gynecologic or pancreatic cancers [4-6]. A further study suggested that perioperative transfusions would affect also survival in cancer patients [7].

In a large retrospective cohort study involving 504,208 consecutive hospitalized cancer patients between 1995 and 2003, Khorana et al. [8] evaluated the risk of thrombosis associated with transfusional

* Corresponding author at: Center of Bleeding Disorders, Department of Heart, Lung, and Vessels, Careggi University Hospital, Largo Brambilla 3, 50134 Firenze, Italy. Tel.: 0039 055 7947587; fax: 0039 0557947794.
E-mail address: giancarlo.castaman@unifi.it (G. Castaman).

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Table 1
Selected risk factors for cancer-associated thrombosis

Categories	Risk factors
Demographics	• Older age • Gender: higher in female • Race: higher in African-Americans and lower in Asians
Cancer-associated	• Site of cancer: brain, pancreas, kidney, stomach, lung, bladder, gynecologic, hematologic malignancies • Stage of cancer: advanced stage and initial period after diagnosis
Treatment-associated	• Hospitalization • Surgery • Chemotherapy and hormonal therapy • Anti-angiogenic therapy • Erythropoiesis stimulating agents • Blood transfusions • Indwelling vascular access

requirement using a discharge database. At least 1 red blood cell (RBC) transfusion was administered to 70,542 patients (14 %) while 15,237 patients (3 %) received at least 1 platelet transfusion. During follow-up, 7.2% patients receiving RBC transfusions developed VTE and 5.2% patients developed arterial thromboembolism (ATE) compared to a 3.8% and 3.1%, respectively, of non-transfused patients. In multivariate analysis, RBC transfusion (odds ratio [OR], 1.60, 95% confidence interval [CI], 1.53-1.67) and platelet transfusion (OR 1.2; CI 1.11-1.29) were independently associated with VTE and to a similar extent with ATE (OR 1.53; CI 1.46-1.61 and 1.55; CI 1.55; CI 1.40-1.71, respectively). 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<0.00001). Thus, both RBC and platelet transfusions appeared to be associated with increased risk of venous and arterial thrombotic events and mortality in hospitalized patients with cancer. However, in this study it was not possible to assess the influence of erythropoiesis stimulating agents, a potential confounding factor, in patients concomitantly receiving ESAs as part of outpatient therapy. Furthermore, data regarding compliance with appropriate thromboprophylaxis were also not available.

The possible mechanisms explaining thrombotic risk associated to red cell transfusion are unclear. An increased iron-catalyzed free radical-mediated oxidative stress [9] due to the large amounts of redox-active iron delivered with tranfusions as well as increased circulating red cell mass which improves hemostasis have been suggested to increase the risk of thrombosis [10]. In addition, depletion of nitric oxide, resulting in vaso-constriction, increased platelet activation [11], inflammatory cytokines and platelet micro-particles could also play a role [12-14].

Whatever the explanation, red cell transfusion may act as an additional risk factor for thrombosis in cancer patients who already have several other risk factors (e.g., age, surgery, site of cancer, presence of comorbidities and chemotherapy) suggesting a conservative approach for supportive treatment in absence of major cardiovascular risk factors associated with anemia.

Similarly, platelet concentrates should be used according to established guidelines, especially in patients with blood malignancies.

Growth factors

Blood transfusions have been largely used to support cancer patients especially to improve quality of life during chemotherapy treatment or to replace blood loss during surgery or because of anatomical lesions associated with tumor. After the introduction of erythropoiesis stimulating agents (ESAs) to improve symptoms associated with chronic renal failure, these agents have also been increasingly used in cancer patients to reduce the need for blood transfusions thus improving quality of life [15]. Anemia can be associated with fatigue, loss of productivity and decreased exercise tolerance and there is some evidence that all these aspects could be improved in cancer patients, similarly to patients on hemodialysis for chronic renal disorders [15]. However, clinical studies have shown that when administered to cancer patients a significant increase of thrombosis occurs [16] and this has been related to the ability of ESAs to trigger signaling pathways in endothelial cells, thus increasing their thrombogenicity [17]. Interestingly there is no consistent correlation of thrombosis risk with rate of hemoglobin rise or dose of ESAs given [18]. Furthermore, VTE occurred in 3/7 patients with myelodysplasia treated with thalidomide associated with darbepoetin-alpha (one patient died of massive pulmonary embolism), leading to definitive trial discontinuation. [19]. The results of this trial raised concerns about the concomitant use of ESAs and anti-neo-angiogenetic agents. However, similar thrombosis rates occurred in 49 patients with multiple myeloma treated with thalidomide and ESA compared to 150 without ESA [20].

Erythropietin receptors have been detected in several types of cancers and it has been suggested that the administration of ESA would also affect survival by promoting the proliferation and survival of the cells expressing these receptors [21]. In a recent metanalysis, mortality rates, VTE rates, and 95% confidence intervals (CIs) were reviewed from 51 clinical trials with 13,611 patients that included survival information and 38 clinical trials with 8172 patients that included information on VTE [22]. Patients with cancer who received ESAs had increased VTE risk (334 VTE events among 4610 patients treated with ESA vs 173 VTE events among 3562 control patients; 7.5% vs 4.9%; relative risk, 1.57; 95% CI, 1.31-1.87) and increased mortality risk (hazard ratio, 1.10; 95% CI, 1.01-1.20). These findings raises concern about the safety of ESA administration to patients with cancer. In the Surveillance, Epidemiology, and End Results-Medicare database, 56,210 patients treated with chemotherapy from 1991 through 2002, aged 65 years or older with colon, non-small cell lung, or breast cancer or with diffuse large B-cell lymphoma and who received chemotherapy were identified [23]. Venous thromboembolism developed in 1796 (14.3%) of the 12,522 patients who received erythropoiesis-stimulating agent and 3400 (9.8%) of the 34,820 patients who did not (hazard ratio = 1.93, 95% confidence interval = 1.79 to 2.07). However, overall survival was similar in both groups [23]. Considering the risk of thrombosis and the hypothetic risk for an increased mortality, the FDA Oncologic Drugs Advisory Committee recommended that ESAs should not be used for patients receiving potentially curative therapies. [24].

In conclusion, while it is clearly demonstrated the increased risk of VTE associated with ESAs, their effect on mortality remains a matter of debate. The current recommendations by FDA, EHA and EORTC underline that hemoglobin target when using ESAs in cancer patients should not exceed 12 g/dL. Treatment with ESAs should be better considered when prolonged myelosuppressive treatment are required to treat the tumor.

Catheter-related VTE in cancer patients

Central venous catheters (CVC) are largely used in many cancer patients to deliver fluids, chemotherapy and supportive treatment. However, these devices are frequently associated with a catheter-related thrombosis (CRT) [25]. The frequency of CRT varies across several studies according to patient selection, type and location of catheter, type of diagnostic approach or monitoring, duration of follow-up and type of event (superficial thrombosis vs occlusive thrombosis) (Table 2). The risk appears grater during the first 10-14 days after insertion [25]. The majority of CRT cases remain subclinical, while clear symptomatic CRT occurs in 1-5% of patients with a CVC [25]. Thus, the methodology used to monitor or diagnose