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Cancer-related venous thromboembolism: insight into underestimated risk factors

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BACKGROUND: Risk factors for cancer-associated VTE include certain cancer types (e.g. pancreatic adenocarcinoma), chemotherapy, and the use of erythropoiesis-stimulating agents, central venous catheters, and surgery. We studied the risk factors for cancer-associated VTE in our institution.

DESIGN AND SETTING: Retrospective analysis of patients with solid cancers treated with chemotherapy at King Khalid University Hospital from 2000 to 2010.

METHODS: We assessed risk factors responsible for VTE, including performance status, age, chemotherapy, use of erythropoietin (EPO), stage of disease and use of a central venous catheter. Patients with other co-morbidities such as diabetes were excluded.

RESULTS: Forty-three (14%) of 306 patients were identified as having VTE, including 111 males and 195 females with a median age of 38 years (range, 13-18 years). Thirty-nine patients had proximal deep vein thrombosis (DVT) and, 4 had pulmonary embolism with no evidence of DVT. Of the 43 patients, 40 patients had stage III or IV disease at the time of VTE diagnosis. Thirty patients were taking erythropoietin (40 000 units/ week); 25 had a hemoglobin level higher than 12 g/dL. All patients were treated with low molecular weight (LMW) heparin and maintained on LMW heparin or warfarin for minimum of 6 months.

CONCLUSION: VTE imposes a great risk to life in cancer patients. Risk factors include age more than 40 years, advanced cancer stage, chemotherapy, use of EPO for anemia and underuse of DVT prophylaxis.

Venous thromboembolism (VTE) is more prevalent in cancer patients, with serious adverse consequences, including high rate of cancer recurrence, long term anticoagulation, poor quality of life and death.[1] Cancer and its treatment can affect all three arms of Virchow's classical triad of causation of thromboembolic disease: alteration in blood flow, damage of endothelial cells, and elaboration of procoagulants. Cancer can affect blood flow by mechanical effects on blood vessels by the tumor as well as by angiogenesis, which is induced by many tumors and may cause the creation of complexes of blood vessels that are aberrant in appearance and have very disordered flow. In fact, flow in these vessels can vary not only in magnitude, but also in direction.[2]

Endothelial cells can be damaged directly by tumors or by chemotherapy. Procoagulants can be increased on the surface of cancer cells, and may also be secreted into the bloodstream. Examples of molecules elaborated by cancer cells that can predispose to disordered coagulation include tissue factor, a vitamin K-dependent cysteine protease that activates factor X, and a mucin procoagulant that activates prothrombin. Furthermore, chemotherapy treatment can cause a reduction in levels of the anticoagulant proteins C and S. Indwelling venous access devices may also predispose to thrombosis by altering blood flow, damaging endothelial cells, and serving as a foreign surface upon which procoagulants can promote thrombosis. In addition, other factors (immobilization, drugs,) can cause dysregulation of the normal mechanisms of thrombosis and hemostasis.[3]

Hormonal therapy can increase the risk of thromboembolic disease. This has been best studied in breast cancer where tamoxifen appear to increase the risk for venous thrombosis. The increase in risk appears to be greatest in postmenopausal patients. An increased risk for arterial thrombosis has also been observed.[4-8]

Erythropoietin (EPO), a glycoprotein hormone,

stimulates erythropoesis by binding to the receptors of erythroid progenitors. In therapeutic doses (about 50 units/kg three times weekly), EPO is used in the treatment of anemia secondary to chronic renal failure (CRF). However, in cancer and chemotherapy-induced anemia, EPO is used in doses up to 500 u/kg weekly. An increased incidence of thrombotic events has been reported in the literature in patients receiving EPO for anemia, particularly when the hemoglobin (Hb) level exceeds 120 g/dL. A rise in the absolute Hb level >12 g/dL or a rate of increase of Hb >1 g/dL every 2 weeks sharply increases the incidence of thrombosis.[9-11]

Various recommendations available in the literature for prevention of VTE secondary to EPO treatment are as follows: (1) the target Hb level should be 12 g/dL, (2) the EPO dose should be reduced by 25% if Hb level approaches 12 g/dL or increases by >1 g/dL in any 2 weeks of the treatment period, (3) if Hb continues to increase >12 g/dL, doses should be suspended temporarily and be reinitiated when hemoglobin begins to decrease, at a dosage that is 25% lower, (4) dosage should be increased by 25% at a frequency of at least 4 weeks interval, (5) the maximal target Hb level should be 12 g/dL, but the goal should be individualized.[11]

Erythropoietin is a risk factor for VTE as it stimulates both red cell production and tumor growth in patients with breast cancer and head and neck cancer and careful monitoring of the Hb level is necessary when using red cell production stimulants in other conditions (including the anemia induced by cancer, renal failure and HIV medications) due to a risk of blood clots that could lead to stroke, heart attacks, deep vein thrombosis, and pulmonary embolism. The deep vein thrombosis risk and pulmonary embolism has also been seen in healthy patients receiving the products to control postoperative anemia.[9,10,12]

PATIENTS AND METHODS

In this retrospective analysis, we studied all cancer patients with solid tumors treated by chemotherapy at King Khalid University Hospital, Riyadh, Saudi Arabia, from 2000 to 2010. VTE was confirmed with duplex ultrasound of the lower limbs and pelvis. Pulmonary embolism (PE) was confirmed with spiral CT scan. The site of VTE was either popliteal, femoral, illieal or vena caval. All patients with PE had echocardiography to assess for pulmonary hypertension. D-dimer was done on an outpatient basis. Presenting symptoms (pain, swelling, dyspnea, cough) or an absence of symptoms, whether inpatient or outpatient, and labs at the time, were noted. The number of patients receiving thromboprophylaxis , type of chemotherapy, performance status, co-morbid conditions (eg, diabetes, ischemic heart disease), stage of disease, duration of anticoagulation, recurrence rates of VTE and overall survival of patients with VTE after anticoagulation were studied.

Inclusion criteria were having a solid cancer and receiving chemotherapy, age 13-85 years, and confirmed VTE and PE. Exclusion criteria were being terminal palliative supportive, bed bound, having pancreatic cancer because of the de novo increase VTE associated with pancreatic cancer, and co-morbidities such as diabetes or ischemic heart disease.

RESULTS

Of 306 cancer patients who received chemotherapy, 165 patients had breast cancer, 73 colon cancer, 45 lung cancer and 23 sarcoma. Forty-three (14%) patients were identified as having VTE, including 165 (53%) with breast cancer, 73 (23%) with colon cancer, 45 (14%) with lung cancer and 23 (7.5%) sarcoma patients. They included 195 (64%) females and 111 (36%) females, and the median age was 38 years with 50% older than 45 years (**Table 1**). Two-thirds had a performance status of 2 or above (**Table 2**). Thirty-nine (91%) patients had proximal limb DVT while 4 (9%) had PE with or without DVT. Thirty-four (80%) patients had pain and swelling as presenting symptoms. Thirty-six (84%) patients were diagnosed as having VTE as inpatients and 7 (16%) as outpatient. Forty (93%) patients received low molecular heparin while 3 (0.9%) patients were receiving heparin followed by long-term warfarin as anticoagulation.

All 43 patients were receiving chemotherapy. More patients (n=11, 25%) were receiving bevacizumab than any other agent. Only 3 (0.9%) patients were on thromboprophylaxis at the time VTE diagnosis, while 4 (10%) patients had diabetes. Thirty-seven (86%) had hemoglobin more than 10 g/dL, while 25 (58%) had Hb more than 12 g/dL at the time of diagnosis of VTE (**Table 3**). Thirty (70%) patients were receiving EPO for anemia, which was started at a dose of 40 000 IU/week when Hb was less than 10 g/dL and not more than 12 g/dL. At the time of diagnosis of VTE, Hb was >12 g/dL. Thrombocytopenia or leucopenia were not observed to be risk factors for VTE in our study. Forty of 43 patients had advanced stage of disease at the time of VTE (93%) (**Table 4**), indicating that an advanced stage of disease may be an important risk factor to be studied in prospective trials. At 2-years post-VTE, the mortality rate was 88% (38/43).

Although controversial, lifelong VTE treatment is recommended after VTE in cancer patients, in our study the median time period for anticoagulation was

6 months. The recurrence rate in our study was 4%. Although studies have shown increased survival post low molecular weight heparin, in our study most of the patients were advanced stage so overall survival was not good as 38 out of 43 (88%) patients who had VTE [H1] died at 2 year interval.[23,24]

In our study, 3 (5%) patients out 56 with performance status (PS) of zero (0) had VTE and 8 (9%) out of 86 had PS 1, 14 (23%) out 60 had PS 2, 13 (16%) out of 82 had PS 3 and 5 (23%) out of 22 had PS 4 at the time of VTE. Overall 32 (74%) patients with VTE had PS 2 or above.

DISCUSSION

Our study was conducted on solid tumor patients who received chemotherapy for the purpose of identifying patients with VTE and possible risk factors. Prophylaxis against DVT remains the most important factor. An increased risk is most generally seen in patients with solid tumors. The underlying biologic factors associated with the increased risk of thrombosis in patients with cancer include the activation of thrombin and fibrin formation both directly by the release of procoagulants by tumor cells and indirectly by the activation of endothelial cells, leukocytes, and platelets by cytokines and the production of a factor X-activating cysteine protease, mucinous glycoproteins, and circulating tissue factor-bearing microparticles (**Figure 1**).[2]

Despite the evidence for increased risk of VTE among patients with cancer and the benefit of prophylactic anticoagulation in specific high-risk settings, surveys of oncologists have demonstrated low rates of compliance with thromboprophylaxis guidelines.[13,14] The American College of Chest Physicians has recently updated general guidelines for VTE prevention, including a limited discussion of patients with cancer.[15] VTE prophylaxis is recommended for both surgical patients with cancer as well as hospitalized patients considered acutely ill. The National Comprehensive Cancer Network provides consensus guidelines on the diagnosis and initial evaluation of VTE in patients with cancer, available therapies for prophylaxis and treatment of VTE and the risks and contraindications of anticoagulation.[16] Several international organizations have also developed guidelines for patients with cancer at risk for VTE.[17,18]

Recommendations for VTE prophylaxis by the ASCO Guidelines include: (1) hospitalized patients with cancer should be considered for VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation; (2) routine thromboprophylaxis is not recommended in ambulatory patients with can-

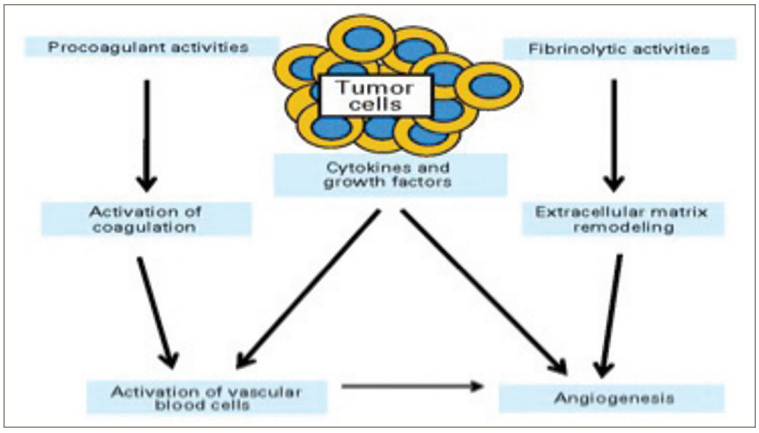

Figure 1. Cancer and venous thromboembolism: diagrammatic representation.[1]

Table 1. Age distribution of all cancer patients and patients with venous thromboembolism.

Age (years)	All patients	Patients with VTE
13-25	26 (8%)	3 (7%)
25-45	123 (40%)	7 (16%)
45-60	95 (31%)	15 (35%)
60-80	45 (15%)	14 (33%)
>80	17 (6%)	4 (9%)
Total	**306**	**43**

Values are number (percent).

Table 2. Performance status of all cancer patients and patients with venous thromboembolism.

Performance Status	All patients	Patients with VTE
0	56 (18%)	3 (7%)
1	86 (28%)	8 (19%)
2	60 (20%)	14 (32%)
3	82 (27%)	13 (30%)
4	22 (7%)	5 (12%)
Total	**306**	**43**

Table 3. Hemoglobin concentration at the time of diagnosis in patients with VTE.

Hemoglobin concentration (g/dL)	No. patients with VTE
<8	0
8-10	6 (14%)
10-12	12 (28%)
>12	25 (58%)
Total	**43**

Table 4. VTE and stage of cancer.

Stage of cancer	
Stage I	0
Stage II	3 (7%)
Stage III	23 (53%)
Stage IV	17 (40%)
Total	**43**

cer, although those with multiple myeloma receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk and warrant prophylaxis; (3) all patients undergoing major surgical intervention for malignant disease should be considered for pharmacologic thromboprophylaxis initiated either preoperatively, or as early as possible in the postoperative period. Extended prophylaxis up to 4 weeks and combined pharmacologic and mechanical prophylaxis may be considered in high-risk patients; (4) LMWH represents the preferred approach for the initial 5 to 10 days of anticoagulant therapy of patients with cancer with established VTE and should be continued for up to 6 months for secondary prophylaxis and indefinitely in patients with active malignancy; and (5) while anticoagulant treatment in patients with cancer without VTE to improve survival is not recommended, patients should be encouraged to participate in ongoing clinical trials evaluating this issue.[16,18]

Patients with cancer hospitalized with neutropenia and presumed infection with documented thromboembolism have a greater in-hospital mortality ($P<.001$).[19] In our study, only 2 patients had platelets count $<75\times10^9$/L and 2 patients had a WBC count less than 1000/μL and more than 500/μL, so no association was seen in our study of thrombocytopenia or leucopenia with VTE.

In a recent study of ambulatory patients with cancer who were receiving chemotherapy, of the 3.2% of patients who died over the first 3 to 4 cycles of treatment, nearly 10% died of thrombosis-related causes.[20] Patients developing symptomatic VTE during chemotherapy have been found to have a greater risk of early mortality (hazard ratio, 4.90; $P<.0001$) than those without VTE.[20] Although all chemotherapies are considered risk factors for VTE, certain biological agents in combination with chemotherapy are also proven to cause more VTE, like bevacizumab.[21] In our study 11 (25%) patients had bevacizumab while being diagnosed as having VTE.

VTE has important impact on overall survival of patients. VTE in cancer patients In one study of more than 100,000 patients with breast cancer, VTE was a significant predictor of decreased 2-year survival including patients with localized disease.[22] In our study all patients were on active chemotherapy when they developed VTE. Two-year survival was low as 38 patients of 43 who developed VTE were dead at 2 years.

The heparins may influence malignant cell growth by inhibiting heparin-binding growth factors that stimulate malignant cell growth, and by inhibiting tumor cell heparinases that influence tumor cell invasion and metastasis, as well as cell surface selectin-mediated tumor cell metastasis.[23-26] Likewise, studies have demonstrated that LMW heparins may inhibit angiogenesis, block thrombin-induced platelet aggregation, inhibit platelet interaction with vascular endothelium, and stimulate platelet production. In our study 40 out of 43 patients used LMW heparin as anticoagulation post VTE.

Erythropoiesis-stimulating agents appear to further increase the risk of VTE in patients with cancer.[12] In our study, of 43 patients with VTE, 30 patients were on EPO for anemia and out of these 25 had hemoglobin more than 12 mg/dL at the time of VTE, emphasizing need for monitoring of hemoglobin carefully while the patient is on EPO for anemia because of the obvious risk of VTE if hemoglobin is more than 12 mg/dL while the patient is on active chemotherapy.

In summary, thrombosis in cancer still poses a great challenge. Poor performance status with an advanced stage of disease, and a lack of VTE prophylaxis remain important risk factors. VTE prophylaxis, although recommended, still remains to be implemented in all eligible patients. Chemotherapy is a known risk factor, but use of EPO during chemotherapy to prevent anemia still remains to be studied, especially when the hemoglobin level is more than 12 mg/dL. We recommend watchful use of EPO for anemia in cancer patients while on chemotherapy with regular thromboprophylaxis.

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