

RESEARCH COMMUNICATION

Frequency, Clinical Pattern and Outcome of Thrombosis in Cancer Patients in Saudi Arabia

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Abstract

Objectives: Thrombotic risk is increased in patients with cancer and there are important implications for those who suffer a venous thromboembolism (VTE). We undertook this study to determine the frequency, clinical patterns, and outcome of VTE in Saudi patients with cancer. **Methods:** Cancer (solid tumors and lymphoma) patients who developed VTE from January 2004 to January 2009 were studied retrospectively. Demographics and clinical characteristics related to thrombosis and cancer were evaluated. **Results:** A total of 701 patients with cancer were seen during the study period. VTE was diagnosed in 47 (6.7%) patients (median age 52, range 18-80 years). Lower limb DVT was the most common type, seen in 47% patients, followed by PE in 19%, and 19% patients had both DVT & PE. Thrombosis was symptomatic in 72% patients while it was an incidental finding on routine workup in 28%. Cancer and VTE were diagnosed at the same time in 38% of patients, and 47% patients developed VTE during the course of disease after the cancer diagnosis. The majority of VTE post cancer diagnoses occurred during the first year (median 4 months, range 1-14). Additional risk factors for VTE were present in 22 (47%) patients and 14 (30%) of these patients were receiving chemotherapy at the time of thrombosis. Only 5 (10.6%) patients were receiving thrombo-prophylaxis at the time of VTE diagnosis. Most common types of tumors associated with thrombosis were breast cancer, non-Hodgkin's lymphoma and lung cancer. The majority of the affected patients (79%) had advanced stage of cancer. After a median follow-up of 13 (range 0.5-60) months, 38 (81%) patients had died. There was no difference in the mortality of patients with symptomatic or asymptomatic thrombosis (82% vs 78.6%). **Conclusions:** Thrombotic complications can develop in a significant number of patients with cancer, and almost half of the patients have additional risk factors for VTE. Thrombosis is usually associated with advanced disease and can be asymptomatic in more than a quarter of cases. Thromboprophylaxis in cancer patients is under-utilized. Community based studies are needed to accurately define the extent of this problem and to develop effective prophylactic strategies.

Keywords: Cancer - deep venous thrombosis - pulmonary embolism - VTE - Saudi Arabia

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Introduction

Venous thromboembolism (VTE) is a frequent complication of cancer due to a hypercoagulable state and is associated with increased morbidity and mortality (Sorensen et al., 2000; Kröger et al., 2006; Khorana et al., 2007; Khorana et al., 2009; Wun & White., 2009). VTE, particularly pulmonary embolism (PE), accounts for a significant number of deaths in cancer patients. The occurrence of VTE in cancer patients varies in different studies and ranges from 1.6%-18% (Sorensen et al., 2000; Chew et al., 2006; Kröger et al., 2006; Khorana et al., 2007; Khorana et al., 2009; Vemulapalli et al., 2009; Wun & White, 2009). Around twenty percent of all patients with VTE have some form of cancer (Goldhaber & Tapson, 2004; Monreal et al., 2006; Imberti et al., 2008). It seems

that VTE is under-diagnosed in cancer patients, as a substantial number of patients may remain asymptomatic (O'Connell et al., 2006; Heidrich et al., 2009). Autopsy studies indicate that up to 50% of cancer patients may have PE present at the time of death indicating a much higher incidence of this complication than is diagnosed during life (Ottinger et al., 1995; Silverstein et al., 1998; Gomes & Deitcher, 2003; Ogren et al., 2006).

The true incidence of VTE in cancer patients is not known due to the presence of a number of different confounding factors (Seddighzadeh et al., 2007). Variable rate of VTE in different studies is likely to be due to multiple factors which include variation in types of cancer and presence of various risk factors for VTE other than the cancer, inclusion of different types of thrombosis such as superficial or arterial thrombosis, and the use of a variety

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of diagnostic and methodological criteria ranging from a clinical suspicion to more invasive procedures (Sallah et al., 2002). Genetic predisposition and racial background appear to be important risk factors for VTE as is evident from the studies showing a low risk of thrombosis in some Asian populations (White et al., 1998; Klatsky et al., 2000; Keenan & White, 2007; Chew et al., 2008).

Therefore, it is important to study the thrombosis risk in cancer patients from different populations for the purpose of risk stratification so the patients at high risk of VTE could be considered for thromboprophylaxis. Thus, identifying clinical characteristics that predispose cancer patients to increased risk of VTE is important to achieve better outcomes. VTE in unselected cancer patients has not been studied in Saudi Arabia. We undertook this study to evaluate the frequency, clinical pattern and outcome of VTE in patients with cancer.

Materials and Methods

We retrospectively studied cancer patients who developed VTE between January 2004 and January 2009, and included patients with solid tumors and lymphomas. History of a thromboembolic event was determined on the basis of information in the patients' records at the primary medical evaluation and follow-up clinic visits. The diagnosis of a new thromboembolic event was based on relevant clinical presentation and confirmation by imaging studies such as Doppler ultrasound, computed tomography and/or ventilation perfusion scans. Only patients with objectively proven VTE were included in the study.

Apart from the demographic characteristics, other parameters studied included type of thrombosis, type and stage of cancer, additional risk factors for VTE present at the time of diagnosis, whether or not receiving chemotherapy at the time of VTE, type of anticoagulant treatment, any recurrences of VTE, and any bleeding complications.

Timing of VTE in relation to cancer diagnosis was noted depending on whether the patients developed VTE before, at the same time or after the cancer diagnosis. Follow up period was calculated from the time of VTE diagnosis till the last clinic visit at the time of data collection, or till the death of the patient.

Cancer patients were not screened routinely for VTE but were investigated if they developed clinical features suggestive of VTE. If the patients were found to have incidental (asymptomatic) thrombosis on routine investigations or staging of the cancer, they were included in the study. Patients who were found to have incidental PE, were screened for DVT in the lower limb and pelvic area.

Results

A total of 701 patients with cancer (solid tumors and lymphoma) were treated during the study period. VTE was diagnosed in 47 (6.7%) of these patients. Characteristics of the patients are shown in Table 1. The most common type of thrombosis was DVT in the lower limbs in 22

Table 1. Patients' Characteristics

Parameter	Number (%)
Age (median, range)	52, 18-80
Gender	
Female	27 (57)
Male	20 (43)
Timing of VTE in relation to cancer diagnosis	
Simultaneous	18 (38)
Before	5 (11)
After	21 (47)
Clinical presentation of VTE	
Symptomatic	34 (72)
Asymptomatic	13 (28)
Other risk factors present for VTE	
Chemotherapy	14 (30)
Erythropoietin	9 (19)
Immobilization	7 (15)
Previous h/o VTE	4 (8.5)
Recent surgery	3 (6)
Others	4 (8.5)
Recurrence of VTE	4 (8.5)
Bleeding complications	5 (10.6)
Type of anticoagulant	
Low molecular weight heparin	23 (49)
Warfarin	20 (42.5)
Others	4 (8.5)

Table 2. Type of Thrombosis

Type of thrombosis	Number (%)
Lower limb and pelvic DVT	22 (47)
PE alone	9 (19)
Both DVT and PE	9 (19)
Upper limb/Subclavian/Jugular DVT	5 (10.6)
Others	2 (4)

(47%) patients, followed by PE in 9 (19%) patients, and 9 (19%) patients had both DVT & PE. Details of the type of thrombosis are given in Table 2.

Eighteen (38%) patients were diagnosed to have cancer and VTE at the same time, and 21 (47%) patients developed VTE during the course of disease after the cancer diagnosis. Five patients developed VTE before the cancer diagnosis while data were missing for 3 patients in this regard. Majority of the VTE post cancer diagnosis occurred during the first year (median 4 months, range 1-30). Additional risk factors for thrombosis were present in 22 (47%) patients. Of the 21 patients who developed VTE post cancer diagnosis, 14 (70%, 30% of total patients) were receiving chemotherapy at the time of VTE diagnosis. Six patients had 2 or more thrombosis risk factors present, usually an additional risk factor along with chemotherapy administration. VTE risk factors other than the cancer present in these patients are shown in Table 1.

Most of the patients received low molecular weight heparin (LMWH) for the initial treatment of VTE but some patients received unfractionated heparin. LMWH was continued in 23 (49%) patients while 20 (42.5%) patients received warfarin for the longer term treatment of VTE. During the later part of the study period, majority of the patients received LMWH for continued treatment. Bleeding complications occurred in 5 patients. Only 5 (10.6%) patients were receiving prophylaxis for

Table 3. Characteristics of the Patients with Asymptomatic VTE

No	Age/ gender	Type of thrombosis	Type of cancer	Stage of cancer	Timing ^a	Receiving ^b chemo	Patient outcome
1	53/M	DVT*	Renal cell	4	Simultaneous	No	Died
2	29/F	PE	Ovarian	3	After	Yes	Died
3	27/F	PE	Gastric	4	Simultaneous	No	Died
4	72/F	PE	Thymoma	2	After	No	Died
5	46/M	PE	GIST	1	Simultaneous	No	Remission
6	20/F	PE	HD	2B	After	Yes	Died
7	30/F	DVT [§]	NHL	4	Simultaneous	No	Remission
8	18/F	DVT [†]	Yolk sac tumor	4	After	No	Stable disease
9	57/F	PE	Rectal	2	After	No	Died
10	39/M	PE/DVT [‡]	Liver	4	Simultaneous	No	Died
11	51/M	PE/DVT [‡]	Colon	3	After	No	Died
12	61/M	PE/DVT [‡]	Breast	3	After	No	Died
13	50/M	DVT [‡]	NHL	3	After	Yes	Died

*Renal vein and inferior vena cava (IVC), §Subclavian & jugular vein, †IVC & iliofemoral, ‡IVC, §Iliofemoral, ‡Splenic vein; GIST-Gastrointestinal stromal tumor; HD-Hodgkins' disease, ^aTiming of VTE in relation to cancer diagnosis, ^bReceiving chemotherapy or not at VTE diagnosis

Table 4. Type and Stage of Cancer in Patients Who Developed VTE

Type of cancer	Number of patients	Early stage	Advanced stage
Breast	9	2	7
NHL	8	2	6
Lung cancer	5	1	4
Colorectal	5	1	4
Upper GI tract	4	1	3
Prostate	2	0	2
Renal	2	0	2
Ovary	3	0	3
Sarcoma	2	2	0
Others	7	1	6
Total	47 (100%)	10 (21%)	37 (79%)

thrombosis at the time of VTE diagnosis.

Thrombosis was symptomatic in 34 (72%) patients while it was an incidental finding on routine workup in 13 (28%) patients. The type of asymptomatic (incidentally diagnosed) VTE was PE in 9 (69%) patients, 3 patients had isolated thrombosis in the abdominal veins, one patient had subclavian and jugular DVT, one patient had PE with inferior vena cava thrombosis, and 2 patients with PE were also found to have a DVT on screening of the pelvic and lower limb veins. The type of cancer, site distribution and other characteristics of patients with asymptomatic VTE are given in Table 3.

The most common type of cancers associated with thrombosis were breast cancer, non-Hodgkin's lymphoma and lung cancer. The type and stage of cancer in patients who developed thrombosis are shown in Table 4. Majority of the patients (37, 79%) with VTE diagnosis had advanced stage (3 or 4) of cancer.

After a median follow-up of 13 (range 0.5-60) months, 38 (81%) of the patients had died. The reason for the overall short median follow up was early death of many of the observed cases. Almost all the patients with advanced stage cancer and thrombosis died except for 2 patients with non-Hodgkin's lymphomas. There was no significant difference found in the mortality of patients between those with symptomatic or asymptomatic thrombosis (82% vs 77%).

Discussion

Cancer patients have an increased tendency to develop VTE and many of these patients have additional risk factors, further increasing the risk of VTE (Sorensen et al., 2000; Chew et al., 2006; Kröger et al., 2006; Khorana et al., 2007, 2009; Wun & White, 2009). There are important implications for cancer patients who develop VTE; these include need for anticoagulation (AC), increased risk of bleeding due to AC and cancer related factors, risk of recurrent VTE, reduction in quality of life, and additional burden on resources (Prandoni et al., 2002; Elting et al., 2004). In addition, cancer patients with VTE have an increased risk of mortality, even after adjusting for the stage of the disease and other factors (Sorensen et al., 2000; Khorana et al., 2007; Chew et al., 2008;), although this observation has been challenged by some investigators (Gross et al., 2007). Thus, VTE diagnosis can have a significant impact on the management and prognosis of cancer patients.

Our study shows that VTE is a significant problem in Saudi patients with cancer. Reported rates of VTE in cancer patients range from as low as 1.6% to as high as 18% (Sorensen et al., 2000; Chew et al., 2006, 2008; Kröger et al., 2006; Khorana et al., 2007; Khorana et al., 2009; Wun & White, 2009; Vemulapalli et al., 2009). Although the rate of VTE in our study does not seem to be very high, we believe the actual rate is likely to be higher due to multiple reasons. Firstly, the rate of VTE may have been underestimated because of the retrospective nature of the study. Secondly, some of the patients with proven thrombosis and strongly suspected to have an underlying cancer, died before the diagnosis was established. Autopsies for diagnostic purposes are usually not carried out routinely in Saudi Arabia because of religious and cultural beliefs. In addition, PE may have been, and was considered to be the terminal event in some of the cancer patients but could not be confirmed and included because of the lack of objective diagnosis and absence of autopsy studies. Therefore, it is reasonable to believe that the actual rate of VTE in Saudi cancer patients is probably much higher than found in our study.

Another important finding from our study is the presence of a substantial number (28%) of patients with asymptomatic thrombosis. Incidental thrombosis is not an uncommon diagnosis in clinical practice, especially in high-risk medical patients. Recent studies indicate a variable prevalence of asymptomatic VTE in cancer patients ranging from 2.1% to more than 6% for PE, and up to 34% for DVT (Gladish et al., 2006; Cronin et al., 2007; Larici et al., 2007; O'Connell et al., 2008; Heidrich et al., 2009; Beck-Razi et al., 2010;). However, the presence of true asymptomatic nature of PE in cancer patients has been challenged as many of the patients considered to be asymptomatic, were found to have some symptoms related to VTE present on careful inquiry (O'Connell et al., 2006).

In our study 28% of patients were found to have asymptomatic thrombosis and majority of these patients had PE while some of the patients were found to have thrombosis in the abdominal and other veins. Survival of patients with asymptomatic thrombosis was not different

from those presenting with symptomatic VTE. Many of the patients had asymptomatic VTE diagnosed during the initial investigations and staging process indicating that asymptomatic VTE may be present in many patients at the time of initial diagnosis. Routine screening for VTE in cancer patients is generally not recommended. However, staging CT can provide a good diagnostic opportunity for investigation of the pulmonary, abdominal and pelvic veins and assessment for DVT and PE is important when reviewing staging CT scans (Cronin et al., 2007). We generally employ therapeutic dose anticoagulation for all cancer patients with asymptomatic VTE and this is the usual practice followed by most of the oncologists. However, one study found that the short term survival without treatment in these patients was not affected (Engelke et al., 2006).

It has now been well established that cancer patients receiving chemotherapy are at enhanced risk of VTE as compared to patients not receiving chemotherapy (Otten et al., 2004; Khorana et al., 2007). Around one third of our patients who developed VTE after the cancer diagnosis, were receiving chemotherapy. A previous study from our centre showed that 14% of patients receiving chemotherapy developed VTE (Al Diab, 2010). Current consensus guidelines do not recommend anticoagulant thromboprophylaxis in cancer patients receiving chemotherapy in the outpatient setting (Khorana et al., 2009). Recently a simple model was proposed to stratify the risk of VTE in ambulatory cancer patients receiving chemotherapy (Khorana et al., 2008). With the availability of this thrombosis risk assessment tool, along with the result of a recently published randomized trial demonstrating benefit for thromboprophylaxis in ambulatory patients receiving chemotherapy, recommendations for VTE prophylaxis in this group of patients are likely to change in the near future (Khorana et al., 2009; Agnelli et al., 2012).

Another important finding from our study is the under utilization of thrombosis prophylaxis in cancer patients. Several studies from around the world have consistently shown a lack of prophylaxis in hospitalized medical patients, including cancer patients (Rashid et al., 2005; Amin et al., 2008). This is a particular problem in the developing countries but also a common observation even in the developed countries (Abba et al., 2004; Rashid et al., 2005; Sleiman et al., 2005; Amin et al., 2008). There are several reasons that might explain why prophylaxis is not a widespread practice on medical and oncology wards and these include; failure to appreciate the risk of VTE in medical and cancer patients, complexity of existing risk assessment models, poor implementation and compliance with the guidelines, and cost issues (Rashid et al., 2005; Woller et al., 2011). Given the underutilization of VTE prophylaxis in cancer patients, an integrated risk stratification checklist along with a pre-printed order sheet for VTE prophylaxis is a useful way of promoting its use, and should be part of the routine assessment of all cancer patients.

In summary, symptomatic and asymptomatic VTE can occur in a substantial number of patients with cancer. Almost half of the patients may have additional risk factors for thrombosis. Our study, the first of its kind

from Saudi Arabia, is important to highlight the magnitude of a common clinical problem. Prospective, community based studies are needed to accurately define the extent of this problem and to identify clinical characteristics of the patients at high risk of developing VTE, with a view to develop and implement effective prophylactic strategies and improve the outcome of cancer patients.

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