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Evaluation of Thromboembolism Risk in Patients with Cancer; Single Center Real-life Data

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is an important cause of mortality and morbidity in cancer patients. Both cancer itself and its treatment have been reported to result in an increased risk of VTE. Several scoring systems have been developed to predict cancer-associated VTE risk. The aim of this study was to prospectively test the validity of the Khorana thrombosis score in predicting the risk of VTE development in cancer outpatients at a single centre.

Methods: One hundred and fifty-two consecutive patients diagnosed with cancer and scheduled to receive outpatient chemotherapy at University of Health Sciences Turkey, İstanbul Training and Research Hospital between August 2012 and August 2013 were included in the study. Khorana risk scores were calculated for each patient at study entry. Patients were then followed up for at least 24 months after diagnosis or until VTE developed.

Results: Thrombosis was detected in 13 of the 152 patients following cancer diagnosis. The median time from diagnosis to thrombosis was 4 months (1-48 months). Thrombosis was of venous and arterial origin in 7 and 6 patients, respectively. The Khorana score failed to differentiate high-risk patients. Scores in patients with and without venous thrombosis were not statistically different (p=0.38).

Conclusion: It is important to identify cancer patients at high risk for VTE to decrease the thrombosis-associated dismal outcome. However, in an outpatient setting, the Khorana score failed to differentiate the target population. This could be partly explained by the heterogeneity and the relatively small number of patients included.

Keywords: Cancer, risk scores, venous thromboembolism

Introduction

Cancer continues to be an important health problem with increasing frequency throughout the world. It is a common cause of death in Turkey comparable to that in developed countries. Both cancer itself and its treatment (i.e., chemotherapy, radiotherapy, surgical interventions, etc.) have been associated with venous thromboembolism (VTE). Several parameters including the primary site and histological features of the tumour, treatment modalities, and metastatic state were indicated to correlate with increased risk of VTE (1,2).

Development of a clinically significant thrombotic event per se and/or complications of the anticoagulant therapy, in particular, bleeding, may interfere with and impede the management of cancer. VTE not only impairs the quality of life of the patient by adversely affecting the general condition but also increases medical expenses (3). Additionally, mortality rates of cancer patients complicated with VTE have been reported to be more than twice those of uncomplicated patients, independent of the stage of the disease (4,5). Thus, VTE is a significant contributor to cancer patients' death and morbidity. To estimate the cancer patients' vulnerability to VTE and differentiate high-risk individuals that would gain advantage from primary thromboprophylaxis, a few scoring methods have been devised.

Primary VTE prophylaxis may decrease fatal vascular complications of deep venous thrombosis (DVT) or pulmonary embolism (PE) and decrease the risk of mortality and morbidity in cancer patients (6). Thus, it would ameliorate the quality of life of the patients and decrease the medical costs. It is therefore of utmost importance to identify patients who would benefit from anticoagulation. In the cancer outpatient setting, symptomatic VTE risk has been estimated to range from 5% to 7%. This rate is similar to the high-risk patients without cancer and have benefited from thromboprophylaxis (7).

Khorana et al. (8) developed a scoring system in their prospective observational cohort study in 2008, which was based on the laboratory

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as well as clinical characteristics of cancer patients at diagnosis and predicted the cancer-associated VTE risk. Primary thromboprophylaxis has been recommended for high-risk patients.

The current study aimed to prospectively assess the reliability of the Khorana thrombosis score in determining the possibility of VTE development in a population of cancer patients in an outpatient setting at a single center where there are no institutional directives for thromboprohylaxis.

Methods

The Study Group

One hundred and fifty-two patients who had been consecutively diagnosed with cancer between August 2012 and August 2013 at University of Health Sciences Turkey, İstanbul Training and Research Hospital were prospectively included in the study. Patients aged 18 or more with a histopathologically verified cancer diagnosis who were scheduled for an outpatient chemotherapy program could enter the study if they provided written informed consent and did not meet any of the following exclusion criteria:

- The history of prior cytotoxic, biological or immunological cancer therapy

- The history of prior radiotherapy

- The diagnosis of acute leukaemia, myelodysplastic syndrome, local non-melanoma skin cancer

- Pregnancy or lactation

- The history of bone marrow transplantation

- The presence of active chronic infection

- The history of previous VTE

- Bedridden or poorly mobilized patients

- The history of recent or current use of anticoagulants or antiaggregants

In Turkey, awareness of cancer-associated thromboembolic events among physicians is scarce and in house directives regulating the prophylactic usage of anticoagulant medications in those with cancer do not exist in most hospitals, including the hospital in which this study was conducted. Consequently, physicians neglect or avoid using anticoagulant therapy, especially if the patient is thrombocytopenic. Thus, this study was designed as a prospective observational study on thromboembolic events in a setting where routine anticoagulant prophylaxis was not practiced on a regular basis.

Method

Each patient's Khorana risk score was calculated at study entrance (8). Following diagnosis, patients were monitored for at least 24 months or until VTE manifested itself. At each visit during chemotherapy and every 3 months after that, patients were surveyed and examined for the presence of VTE (DVT, PE, abdominal venous thrombosis, etc). Confirmatory coagulation and imaging tests were performed in cases of clinical suspicion.

Statistical Analysis

The statistical evaluation was done using SPSS version 15.0. Results were given as mean ± standard deviation in the presence of a normal distribution. Nonparametric parameters were reported as medians. To compare the two groups, chi-square and Mann-Whitney U tests were utilized. $P<0.05$ was accepted to be statistically significant.

Results

Patient characteristics are listed in Table 1. Breast cancer was the most frequent type of cancer in the study group (42.9%), followed by colon cancer (23.8%) and lung cancer (11.4%). A complete list of malignancies diagnosed in the recruited patients is given in Table 2. Of the 152 patients in total, 98 (64.5%) and 54 (35.5%) had Eastern Cooperative Oncology Group (ECOG) performance scores of 0/1 and 2/3, respectively. Khorana risk scores were found 0 in 52 patients (34.2%), 1-2 in 84 patients (55.2%), and 3-4 in 16 patients (10.5%) (Figure 1). Following the cancer

Table 1. Patient Characteristics

The number of patients (n)	**152**
Age [year, mean (range)]	57 (23-84)
Gender (n, M/F)	53/99
Stage (n, early /metastatic)	87/65
ECOG [median (range)]	1 (0-3)
Radiotherapy (n, %)	63 (1.4)
Hormonal therapy (n, %)	30 (19.7)
Surgery (n, %)	112 (73.7)
The complete clinical response (n, %)	94 (61.8)
Relapsed cases (n, %)	15 (9.9)
Patients with catheter (n, %)	34 (22.4)
Patients with thromboembolic events (n, %)	13 (8.6)
Thrombosis (n, venous/arterial)	7/6
Time from diagnosis to thrombosis [months, median (range)]	4 (1-48)
Thrombosis score [median, (range)]	1 (0-4)
Coexisting disease (n, +/-)	61/91
Haemoglobin* (g/dL)	12.17±1.50
White blood cell count* (/mm^3, mean ± SD)	8160.92±2739.06
Platelet count* (/mm^3, mean ± SD)	355368.4±162309.6
LDH* (U/L, mean ± SD)	127.66±42.50
HDL* (mg/dL, mean ± SD)	50.93±14.38
Total cholesterol* (mg/dL, mean ± SD)	207.49±46.39
Triglyceride* (mg/dL, mean ± SD)	143.0±65.70
CRP* (mg/dL, mean ± SD)	1.87±3.33
D-dimer*(mg/dL, mean ± SD)	2.03±2.88
BMI* (mean ± SD)	27.47±5.10
Progression-free survival (months, mean ± SD)	18.87±15.94
Overall survival (months, mean ± SD)	20.58±17.89
The status at the last follow-up [n, dead/alive/unknown (%)]	18/112/22 (11.8%/73.7%/14.5%)

*At the time of diagnosis, M/F: Male/Female, ECOG: Eastern Cooperative Oncology Group performance score, SD: Standard deviation, BMI: Body mass index, LDH: Lactate dehydrogenase, HDL: High-density lipoprotein, CRP: C-reactive protein

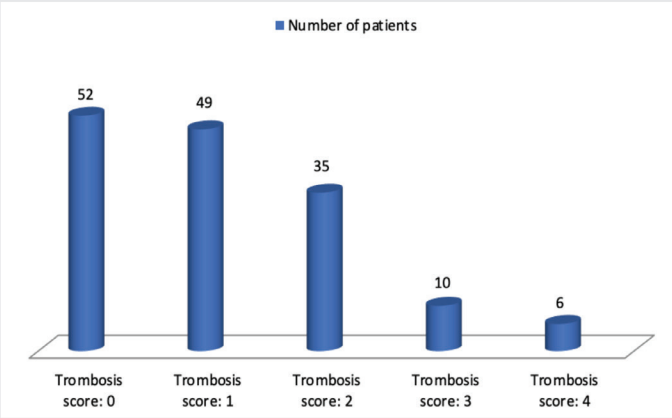

Figure 1. Distribution of Khorana scores

Table 2. Sites of tumour origin

Origin of the tumour	The number of patients, (n, %)	
Bladder	2	(1.3)
Breast	56	(36.8)
Colon	36	(23.7)
Gall bladder - intrahepatic bile ducts	2	(1.3)
Kidney	1	(0.7)
Larynx	1	(0.7)
Lung	16	(10.5)
Lymphoma	3	(2.0)
Multiple myeloma	1	(0.7)
Oesophagus	1	(0.7)
Ovary	8	(5.3)
Pancreas	2	(1.3)
Prostate	3	(2.0)
Rectum	4	(2.6)
Stomach	13	(8.6)
Testis	1	(0.7)
Thyroid	1	(0.7)
Uterus	1	(0.7)

diagnosis, clinically significant thrombosis was observed in 13 of 152 individuals. Median time from diagnosis to thrombosis was 4 months (1-48 months). Thrombotic attacks were of arterial and venous origin in 6 and 7 patients, respectively. Patients with and without VTE did not have substantially different median Khorana scores (p=0.38). In cases with VTE, Khorana scores were 1 in 46% and 2 in 23% of the patients. Among the group without VTE, the percentage of patients with 0, 1 and 2 Khorana scores was found to be 91%. Venous thrombosis was detected in one of the 52 patients with score 0, in 3 of the 49 patients with score 1, in 2 of the 35 patients with score 2, in none of the 10 patients with score 3, and in only 1 out of 6 patients with score 4.

Patients with arterial thrombosis consisted of 5 females and 1 male patient, with a median age of 65. The median thrombosis score was 1.5 (1-3). Platelet counts, Khorana, and ECOG performance scores at diagnosis were found to be statistically significant between patients with and without arterial thrombosis (p values: 0.047, 0.044, and <0.001, respectively). There was a higher possibility of arterial thrombosis with advanced age, male gender, and a history of surgical intervention (p values: <0.001, 0.02, and 0.005, respectively).

Patients with venous thrombosis consisted of 5 females and 2 males with a median age of 55 years and a median thrombosis score of 2 (1-3). Khorana thrombosis scores did not differ in patients with and without venous thrombosis (p=0.38). However, overall and progression-free survival durations were significantly lower in patients with venous thrombosis (p values: 0.021 and 0.022, respectively). Neither age, gender, BMI, presence of metastatic disease, nor the thrombotic risk score predicted venous thrombosis (p>0.05).

Surgical intervention within 4 weeks before diagnosis was found to have a significant impact on thrombosis development (p=0.02). Neither radiotherapy nor the type of chemotherapy was linked to increased risk of thrombosis (p=0.16 and 0.26, respectively). However, we observed a marked association between the presence of active and/or recurrent disease, ECOG performance score, and thrombosis occurrence. The use of a central venous catheter and/or concomitant comorbidities was not linked to the occurrence of VTE (p>0.05). Likewise, no significant difference could be identified in haemoglobin, leukocyte, platelet, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglyceride, D-dimer, and C-reactive protein (CRP) levels at the time of diagnosis between patients with and without venous thrombosis. However, D-dimer and CRP levels were noticeably higher in patients with thrombosis when arterial and venous thromboses were taken together (p values: 0.047 and 0.03, respectively).

Discussion

Both morbidity and death in cancer patients are significantly influenced by VTE. The management of thrombosis may lead to delays for treating cancer and may result in life threatening complications such as bleeding. This, in turn, not only impairs the general condition of the patient but also increases the medical costs (5). Additionally, mortality rates have been found to be twice as high in patients complicated with VTE than in those without venous thrombosis (9). Prophylactic treatment with anticoagulants would decrease the rates of mortality and morbidity and improve survival of patients with cancer (10). Most of the previous studies dealing with thromboprophylaxis mainly included patients with metastatic breast and lung cancer and those with central venous catheterization (11-15).

Vascular complications with high rates of mortality such as DVT and PE can be avoided with primary VTE prophylaxis, which usually results in decreased rates of mortality and morbidity in high-risk individuals such as those who have cancer (6). Thus, by giving primary anticoagulant prophylaxis, one can ameliorate cancer treatment, improve the quality of life, and decrease medical costs. It is important to define a high-risk population to prevent the negative outcome of VTE. In cancer outpatients, symptomatic VTE is reported to be between 5% to 7%, which is similar to the rate of patients without cancer that have been shown to have benefited from thromboprophylaxis (e.g., hospitalized patients

receiving medical therapy) (7). In our study, venous thrombosis occurred at a rate of 4-6% and 8.5% of patients had both arterial and venous thrombosis.

Khorana et al. (8) developed a scoring tool to predict VTE risk for pofents with cancer by us clinical and laboratory data of prospectively followed 2071 outpatients with cancer. They recommended thromboprophylaxis for cancer patients with a high risk for developing VTE. In our study, we used Khorana risk scoring to assess the possibility for developing VTE in 152 outpatients with cancer when it was initially diagnosed. The patients were followed for an average of 17 months. Thrombotic attacks of arterial (6 cases) and venous (7 cases) origin were observed in 13 patients during follow-up. The site of cancer has been linked to VTE occurrence in previous studies. Cancers originating from the brain, pancreas, stomach, kidney, over, and lungs and hematological malignancies, especially lymphomas, have been reported as the leading causes of VTE (2,16). In a case control study, VTE was observed at the highest rate in patients with hematological malignancies, followed by the lungs and gastrointestinal system (1). In our study, the most frequent sites of involvement was the gastrointestinal system, lungs and blood. The highest risk of VTE development is in the first few months after the diagnosis (1). Between the cancer diagnosis and the thrombotic episode in our cohort, there was a 4-month median interval.

In large cohort studies, the stage of cancer is an important risk factor underlying VTE (9). However, other studies including outpatients with ovary cancer could not demonstrate any significant relationship between stage and VTE occurrence (17). Similarly, in our study, we could not reveal any correlation between stage and the risk of thrombosis. This can be explained by the relatively good performance status of our cohort with a median ECOG score of 1.

Performance status is a surrogate marker for immobility, another well-defined risk factor for VTE (10). In a prospective study, which consisted of lung cancer patients receiving chemotherapy, the VTE rate was found to be 31% in patients having poor performance status and 15% in the group having good status (18). Although there was no statistically significant difference, another investigation on outpatients with cancer discovered that the incidence of VTE was higher in patients with relatively poor performance status. Over 90% of the patients who were included in the analysis had extremely good performance status, which helped to explain this (2). Poor performance status is accepted to be associated with recurrent VTE occurrence in cancer patients (19). A statistically significant correlation between high ECOG performance scores and the potential for thrombosis was identified in our research. Subgroup analysis revealed that high ECOG scores predicted a significant risk of arterial thrombosis ($p \leq 0.001$) at our hands but not for venous thrombosis ($p=0.06$).

Recent findings indicate that VTE risk persists at high rates for a long time postoperatively (20). Khorana et al. (8), however, could not identify surgical intervention as a risk factor in their cohort, which was then explained by the fact that almost all patients were on postoperative thromboprophylaxis. In contrast, individuals with a history of surgical procedure had a higher prevalence of arterial but not venous thrombosis, according to our cohort analysis.

VTE is a major issue for hospitalized and old cancer patients (>65 years old) (21). However, age per se has been shown not to be a significant risk factor for VTE development in cancer outpatients if the performance status is good (2). In our cohort, age and gender were not related to thrombosis. However, when only the group of patients with arterial thrombosis was evaluated, male gender and age were noted as risk variables.

In a prospective observational trial on those who are undergoing chemotherapy for cancer, high platelet counts before treatment were found to be connected to an increase in VTE occurrence (2). Another retrospective trial, which included hospitalized cancer patients, found platelet counts over 350000/mm^3 to be predictive for VTE development (22). Recent studies have shown an association between white blood cell (WBC) counts and vascular events (23). In patients with myeloproliferative diseases, WBC counts were clearly shown to be a risk factor for venous thrombotic events (24). In our cohort, we could not identify any significant relationship between VTE occurrence and WBC and platelet counts at diagnosis. On the other hand, it was discovered that a significant predictor of arterial thrombosis was high platelet counts. However, this finding should be cautiously approached as the number of patients with arterial thrombosis is small and confounding factors such as comorbidities might have interfered with the outcome.

D-dimer levels are typically observed to be higher in cancer patients (20), which has been demonstrated to be a substantial predictor for recurrent VTE (19). Ay et al. (25) pointed out that adding plasma levels of D-dimer and soluble P-selectine to the scoring may improve the potential of the Khorana risk scoring system in predicting the risk of VTE. Our results also indicate a statistically significant association between D-dimer concentrations at the time of diagnosis and the risk of thrombosis. Similar to D-dimer, elevated CRP concentrations (>400 mg/dL), a predictor of inflammation, were observed to be associated with VTE in cancer patients (3). Our cohort study also found that high CRP levels were significantly related to thrombosis.

We observed clinically significant VTE events in our study without performing a routine screening for thrombosis. Although there is a non-negligible probability of recurrent thrombosis when VTE is unintentionally found, a recently published meta-analysis of cancer-related thrombosis demonstrated a low recurrence rate with incidental VTE (26). However, evidence is still conflicting and inadequate to suggest routine radiological and laboratory screening for thrombosis in cancer patients.

Khorana risk score is one of the recommended tools in the guidelines for preventing VTE in cancer patients who are outpatients (27,28). For real-life data emerge, risk scores should be applicable in general medical practice. However, a recent study showed that no high-risk cancer outpatient received thromboprophylaxis (29). On the other hand, the method of assessing the risk of bleeding in patients with an elevated likelihood of thrombosis, the duration of prophylactic anticoagulation, and the types as well as the doses of prophylactic anticoagulants remain unclear. Because thrombocytopenic patients and individuals having creatinine clearance below 30 mL/min were removed from the studies, the use of these thrombosis assessment tools in hematology practice

seems limited. More prospective, randomized studies are needed on these issues.

Study Limitations

The main limitations of this study are the heterogeneity of the cancer types and the relatively small number of patients included.

Conclusion

Thrombosis is an important issue contributing to the dismal outcome of cancer. Therefore, patients who are at a high risk of developing thrombosis should be identified. The available data point to the usage of thromboprophylactic medications for cancer patients who have a higher risk of thrombosis. The risk of VTE in cancer patients has been predicted using various risk assessment systems. We used Khorana risk scoring to assess its predictive potential and tested other risk factors that could indicate increased risk for arterial as well as venous thrombosis in a prospective real-life setting in patients with cancer who were not on thromboprophylaxis. Our results, in general, are in line with the current literature. Khorana scores, however, could not fully identify patients at risk in our cohort. Although statistically not significant, thrombosis frequency was higher in patients with higher scores (Khorana 3 and 4). This may be described by the tiny sample of patients in the cohort.

Ethics Committee Approval: The study was reviewed and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 173, date: 07.09.2012).

Informed Consent: Informed consent forms were obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.E., R.U.G., M.H.E., M.C.A.; Concept - S.E., M.H.E., M.C.A.; Design - S.E., M.H.E.; Data Collection or Processing - S.E., R.U.G.; Analysis or Interpretation - S.E., M.H.E.; Literature Search - S.E., M.H.E.; Writing - S.E., M.H.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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