Original Articles/นิพนธ์ต้นฉบับ

Venous Thromboembolism in Solid Cancer Patients.

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Abstract

Background: Venous thromboembolism (VTE) is a frequent and significant complication of cancer. Many previous studies showed that malignancy was the most common acquired cause of VTE which potential caused many effects on cancer patients themselves, treatments and prognosis.

Objectives: To identify the incidence of VTE, risk factors and review the characteristics, clinical course including VTE treatment of patients with solid cancer who had VTE.

Methods: Non-gynecological solid cancer patients with VTE, treated at Ramathibodi hospital during January 2003 to December 2007, were enrolled in this study. Patient characteristics were obtained from their medical records with emphasis on primary site of cancer, staging, demographics, type of cancer treatment and circumstantial vascular risk factors.

Results: There are 178 cancer patients included in this study. The mean age of the patients is 58.77 years. It is equally by sex. Among the patients, lung, colorectal, hepatocellular carcinoma (HCC), breast cancer and cholangiocarcinoma are the top five most common cancers respectively. Our study shows that cancer patients with VTE tend to have advanced stage, higher recurrence and poorer response to treatment. Adenocarcinomas are the most common type of cancer in our study. Approximately 50% of our patients developed VTE at the same time with cancer diagnosis. The latter had developed this condition for the mean of 13.3 months later from that time. PORT implantation and some primary tumors are related with sites of VTE. Median time from VTE presentation until death is 22.3 months. Female has significantly better prognosis than male patients ($p=0.0123$). Breast and colorectal cancers also have the same than others too ($p<0.001$). One third of the patients treated with anticoagulant had major bleeding complication and 60% of them occurred within 1 month after warfarin usage.

Conclusion: Cancer patients with VTE have poor prognosis and tend to have more advanced stage and poorer response to therapy. Moreover, they might increase bleeding complication from anticoagulation therapy. However, our populations are too small to determine other risk factors which previously reported. Large number of patient needs to be more study in this condition.

Keywords: Venous thromboembolism, Solid cancer

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Introduction

Hypercoagulable state has been demonstrated in cancer patients. This condition was first described by Trousseau in 1865. This topic has been extensively reviewed by many studies[1,2]. Approximately 20% of all new venous thromboembolism (VTE) events are related with malignancy[2]. Clinical VTE occurs in 11% of cancer patients and increases the likelihood of death by 2 to 8 fold[3,4]. Many researchers have proposed some types of cancer provoke a higher risk of VTE[3,5-6]. For example, pancreatic cancer and brain tumors show association with a higher risk of VTE than others. In addition, incidence of VTE is higher in advanced stage of cancers compared with early stage cancers[6,7]. The extensive of thrombosis has been demonstrated in advanced cancer status in many types of cancer such as prostate, lung and ovarian cancer and correlated with poor prognosis[6-10]. Many risk factors of VTE related with cancer treatment have been demonstrated including administration of systemic chemotherapy[11-13], usage of tamoxifen[13,14], types of surgery and duration of hospitalization[15-17]. Usage of intravenous devices for cancer treatment also increases risk of VTE[14,18,19]. Therefore, we operated this study to review the incidence, patient characteristics and impact of VTE occurrence in cancer patients treated in Ramathibodi hospital.

Material and Methods

Patients and study design

We retrospectively reviewed database of all cancer patients who had a VTE treated at Ramathibodi hospital from January 2003 to December 2007. The patients were collected by using the International Classification of Diseases (ICD), 10th version. We determined C00-C97 as a group of malignant neoplasm excepting C51-C58 of female genital organs that has already been studied. For searching VTE, we use I80-I82 and I87. All patients who were older than 18 years old and had confirmed diagnosis of cancer and VTE were included in this study. The research was approved by the ethic committee.

Histological diagnosis, cancer staging and patient characteristics including ECOG performance status (ECOG-PS), Body mass index (BMI) and their underlying disease were collected from chart reviewed. The exclusion criterions were history of familial hypercoagulability and previous VTE of the patients. We used national census to find the patients' date death.

VTE was documented by using imaging studies such as Doppler-ultrasonography for deep vein thrombosis (DVT), radionuclide lung scan (V/Q scan) and/or CT angiogram for pulmonary embolism (PE). We also explored the treatment of anticoagulant for VTE including its effectiveness and complication.

Statistical methods

We calculated on overall response of treatment and overall survival (OS) of the cases. Eligible patients were considered for analysis. Lived patients were censored as their last follow-up day. OS is defined from the first occurrence of cancer to the date of any death or of the last follow-up instead of absent date of death. Survival curves were estimated to demonstrate OS using the Kaplan-Meier method. Continuous variations were presented as mean and standard deviation. The statistically significant level is set at $P < 0.05$. Analysis was performed by using EPI INFO (Version 3.5.1) software.

Results

Patient Characteristics

One hundred and seventy eight cancer patients who had at least one episode of VTE in their lives were collected. Half of cases (51.1%) were female. Mean age was 58.77 year old (ranging from 20-91 years old with). ECOG-PS was documented only 27 patients' medical records. Most of them were ECOG-PS ≥ 3. Only 116 patients had their height and weight

completely filled in medical records. By that reason, only 116 patients were able to calculate BMI. Mean BMI was 22.9 at the time of VTE diagnosis. Only 17 of 116 patients (14.65%) were diagnosed overweight by BMI (BMI ≥26). Hormonal therapy such as tamoxifen, anti-androgen and oral contraception were found only 17 patients. Thirty one percents of all patients had co-morbid diseases such as diabetes, hypertension and past history of cerebrovascular accident (CVA). Most of them (72.5%) had only one disease.

Types of cancer

The type of cancer in our study was shown in Table 2. Among those patients with VTE, lung cancer, colorectal cancer, hepatocellular carcinoma (HCC), breast cancer and cholangiocarcinoma were the common type of cancer (39, 27, 22, 15, 14 cases) respectively. Only 95 from 178 patients had document of their histological tissue diagnosis. Adenocarcinoma was the most common tissue diagnosis among those patients (67 from 95 patients) and the second was squamous cell carcinoma (12 from 95 patients). Eleven of all patients had cancer originated from abdominal cavity, pelvic cavity, back and lower extremity in which are high risk to develop VTE by site. 2 cases of adenocarcinama and 4 cases of squamous cell carcinoma were found. The rest of the patients in this group had soft tissue tumors (4 cases of malignant fibrous tumor and 1 case of gastrointestinal stromal

Table 1. Demographics and cancer status of patients affected with VTE

Demographics and cancer status	Number (%; n = 178 cases)
Mean age: (range/years)	58.77(20-91) SD= 32.6
Sex	
male	87
female	91
Final status	
Death	153
Alive	25
Cancer status when VTE diagnosed	
Occurred the same time of cancer diagnosis	80 (44.9)
Occurred after diagnosed cancer	52 (29.2)
Occurred before 1st recurrence	1 (0.6)
Occurred the same time of 1st recurrence	15 (8.4)
Occurred after 1st recurrence	19 (10.7)
Occurred after 2nd recurrence	11 (6.2)
T staging	
1	1 (0.5)
2	4 (2.2)
3	16 (9)
4	45 (25.3)
unknown	112 (63)
M stage	
0	15 (8.4)
1	90 (50.6)
unknown	73 (41)

tumor (GIST)). There were 27 genito-urothelial cancer patients (13 cases of bladder cancer, 7 cases of renal cell cancer and 7 cases of prostate cancer). Only 105 patients had completed document of cancer staging. 90 from 105 patients presented with distant metastatic disease (Table 1). There were 52 patients who developed second primary cancers or recurrence of primary cancer. 34 cases were in the latter group. 73 patients were treated with chemotherapy and approximately 68.5% were treated with palliative intent. 65 patients received radiotherapy, 54 cases (83.1%) were treated with palliative intent. Unfortunately, 47.8% of all patients developed progressive disease after cancer diagnosis (Table 1).

Venous thromboembolism

In our study, 80 patients (44.9%) developed VTE at the same time of cancer diagnosis. 52 patients (29.2%) developed VTE after diagnosis of cancer. The rest of them developed VTE later at the time of cancer recurrence (Table 2).

The most common site of VTE is unilateral leg [84 (47.2%)], followed by pulmonary embolism [23 (12.9%)] (Table 3). Only 3 patients with PORT implantation developed VTE at that same site of jugular vein. Eleven of all 12 HCC patients developed VTE at portal vein and 6 of 7 Renal cell carcinoma (RCC) patients developed VTE at inferior vena cava (IVC).

Total 153 patients died after diagnosis of cancer. Only 148 patients have documented the date of death. Mean survival in those patients is about 7 months. Only 18 patients developed VTE during hospitalization and most of them developed VTE after operation (15 cases).

Table 2. Types of cancer affected with VTE

Types of cancer	Number of cases (%; n=178)
Lung	39 (21.9)
Colon and rectum	27 (15.2)
Hepacellular carcinoma	22 (12.4)
Breast	15 (8.4)
Cholangiocarcinoma	14 (7.9)
Bladder	13 (7.3)
Cancer in abdomen, pelvic cavity, back and extremity	11 (6.2)
Adenocarcinoma	2 (1.1)
Squamous cell	4 (2.2)
Fibrous tumor	4 (2.2)
GIST	1 (0.55)
Prostate	7 (3.9)
Renal cell carcinoma	7 (3.9)
Esophagus and stomach	6 (3.3)
Brain tumor	4 (2.2)
Head and neck	4 (2.2)
Pancreas	3 (1.7)
Miscellaneous (Germ cell, Thymoma, Thyroid)	5 (2.8)
Carcinoma without tissue diagnosis	1 (0.55)

GIST: gastrointestinal stromal tumor

Table 3. Sites of venous thromboemblism and status of cancer patients

VTE site	Number of cases (%; n=178)
Unilateral leg	84 (47.2)
Pulmonary Embolism	23 (12.9)
Bilateral legs	22 (12.3)
Inferior Vena Cava	18 (10.1)
Portal Vein	13 (7.3)
Jugular vein (left, right)	8 (4.5), 5 (2.8)
Superior Vena Cava	4 (2.2)
Renal	1 (0.6)
Total	**178 (100)**
Two concomitant sites of VTE	27 (15.2)

VTE: venous thromboembolism

Treatments

Fifty three of all patients (29.8%) received only best supportive care and no specific treatment for their cancer. 93 patients were treated with anti-coagulant. The common regimen was low molecular weight heparin (LMWH) for initiation then switched to warfarin (48.4%). Continuous injection of LMWH was given about 35.5% of treated patients (33 patients). Only 12 patients (12.9%) were the latter groups treated warfarin as single agent. 29 cases (31.2%) developed bleeding complication after started anticoagulant, mostly warfarin and most of them had a major bleeding. Bleeding complication occurred about 60% of patients within 1 month after started anticoagulant. Our 6 patients developed clinical recurrence of VTE as new development of enlargement of previous affected legs for 4 patients and of dyspnea for 2 patients that had suspect of PE. These symptoms were occurred within 1 month after treatment. All of them were not definite proved with imaging. Six cases underwent inferior vena cava (IVC) filter placement due to contraindication of anticoagulant. Unfortunately, most of these cases have had short survival after this operation.

Survival

We found that female patients have a better survival than male patients significantly (P = 0.0123) (Figure 1). Median survival of female and male are 28.7 and 12.4 month, respectively. Survival curve between age < 60 or older has a trend of better survival but not reach statistically significantly after 5 years of follow up. Sites of VTE have no influence on their survival. Breast cancers and colorectal cancers have a better survival than the other types of cancer statistically significant (P = 0.007) (Figure 2). 153 of 178 patients (86.4%) died at the end of this reviewed.

Discussion

This retrospective study is conducted to determine patient characteristics, types of cancer and prognosis of VTE in solid cancer patients in our institution. We excluded gynecological malignancies from this study because they already had been studied and published by our group[20]. In our study, advance stage of cancer as more T and N stage, multiple lines of chemotherapy and refractoriness of cancer are risk factors of VTE as shown in other previous studies[6-7,21,26]. The other confounding factors such as

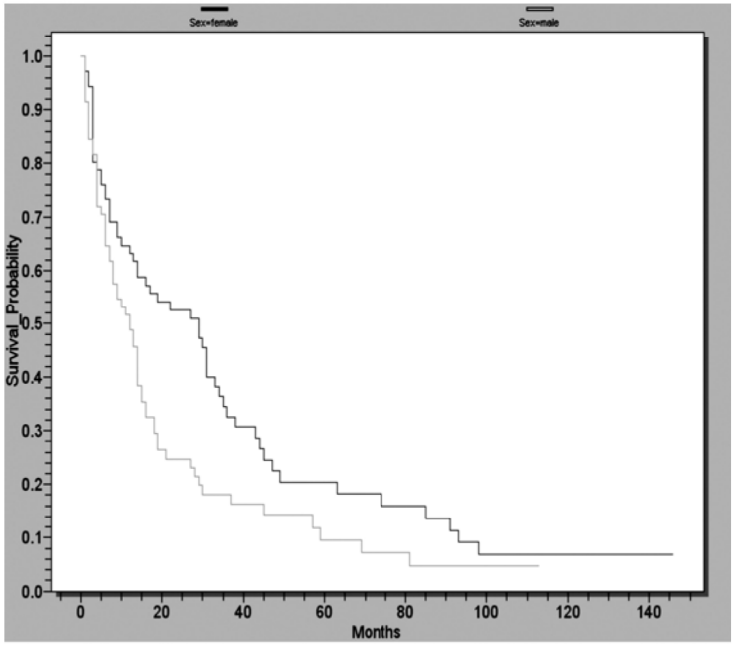

Fig.1 *Kaplan-Meier curve demonstrating difference between sex upon survival.*
Median survival male= 12.4 months
Median survival female= 28.7 month
p = 0.0123

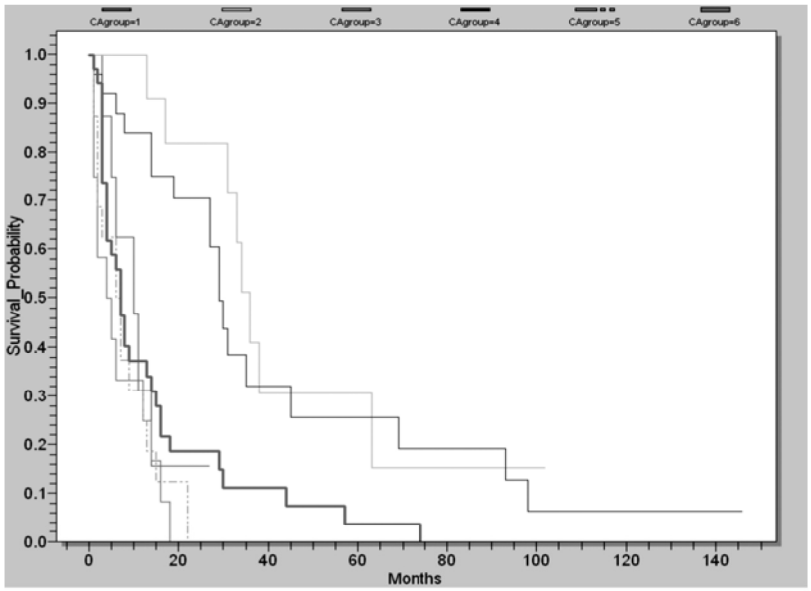

Fig.2 *Kaplan-Meier curve demonstrating difference between five most common types of cancers upon survival.*

Median survival of CA Lung = 7.2 months
Median survival of HCC = 5.9 months
Median survival of Cholangiocarcinoma = 4 months
Median survival of CA Bladder = 10 months

Median survival of CA Colon and CA Rectum = 29.6 months
Median survival of CA Breast = 36.1 months

Between two groups p= <0.001

hormonal usage, obesity and high ECOG-PS that correlated with higher risk of VTE have not shown in our study. However population in our study is too small to demonstrate a difference.

We found that among of all kinds of cancer, the most common types of cancer which developed VTE in our study were lung cancer, colorectal cancer, HCC, breast cancer and cholangiocarcinoma respectively. In contrast to previous published studies[6,22,23], we found that pancreatic cancer and brain tumor in our study are less common. Interestingly, the types of cancer which developed VTE in our study are common cancers in general Thai population such as lung, colorectal, HCC, breast, cholangiocarcinoma and prostate cancer. But, some studies claimed that breast cancers had low risk to VTE[24,25].

Adenocarcinoma subtype is highly associated with VTE in our study and also founded in previous published data[22,26]. The incidence of VTE occurs mostly at the same time of cancer diagnosis is shown in our study comparable with previous study[24,27-29]. Overall survival of cancer patients is approximately 1 year later from time of VTE presentation and comparable with our study (7 months)[4,6,25,27].

Hospitalization provokes incidence of VTE in cancer patients in many studies but our study has not demonstrated this risk factor probably because of small numbers in this condition (18 cases)[28]. But 16 of these 18 patients with hospitalization are post operation concordant with some other studies[29,32]. We have only few patients who use PORT implantation to determine its impact on VTE occurrence. Our study shows the sites of VTE are associated with primary site of cancers such as HCC increases risk of portal vein thrombosis, RCC increases risk of IVC thrombosis but only small number of patients.

Our study demonstrates that female patients have longer survival twice times than male patients. For the type of cancers, Breast cancers and colorectal cancers have better survival than other solid tumors probably from their natural history and effective treatment in these diseases.

Progression and recurrence of VTE and adverse effect of bleeding complication of anticoagulant are major problem in those with malignancy. Prandoni and his colleagues found that recurrent VTE was 20.7% in 1 year and major bleeding was 12.4% in their cases[30]. Our patients developed equally recurrence of VTE as 6 of 29 patients who treated with warfarin (20.68%) but within only 1 month. Major bleeding complication was found about 9.5% after anticoagulant in our study. About 30% of cases treated VTE with anticoagulant have major bleeding complication within a week of initiation heparin.

ACCP 2004 and NCCN guild-line suggest that using LMWH in cancer patients with VTE is safer[31]. We started LMWH initially then switch to warfarin for a long term treatment on the most of the cases. The reason for less use of LMWH as international guild-line is according to our country's economy. The further management in recurrent VTE after failure of warfarin is not widely concluded[32,33]. In our institute, the further treatment in those cases are the same as previous published is to use heparin especially LMWH for resistant cases. Our study has not enough data to show how really recurrence of VTE happens by provable imaging or autopsy. As widely knowledge, LMWHs is safe and convenient to use recommended for cancer patients than warfarin. After failure of LMWH treatment or contra-indication established, placing of a vena cava filter is used[34]. There is a small part of such treatment reviewed in our finding and less data to represent that benefit.

Our study demonstrates as many prior studies that cancer patients with VTE have a grave outcome but questionable about it was caused by VTE or malignancy. Prostate and breast cancer have a better outcome than other cancers. However it can explain by their better prognosis compared with prognosis of other cancers.

Our study has several limitations such as small number of patients, retrospective study design. We missed some patient characteristics to determine risk of VTE. Because of a small number of patients, it is under powerful to show any statistically significant difference among the stratified risk factors. In our study, only female sex has a better impact on patients' outcome.

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Original Articles/นิพนธ์ต้นฉบับ

ภาวะหลอดเลือดดำอุดตันในผู้ป่วยโรคมะเร็งก้อนทูม

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บทคัดย่อ

บทนำ: Venous Thromboembolism (VTE) เป็นภาวะแทรกซ้อนที่พบได้บ่อยและสำคัญของโรคมะเร็ง หลายการศึกษาก่อนหน้านี้ แสดงว่าโรคมะเร็งก็เป็นสาเหตุสำคัญของการเกิด VTE ซึ่งจะก่อให้เกิดผลกระทบมากมายในผู้ป่วยมะเร็งเองการรักษาและพยากรณ์โรค

วัตถุประสงค์: เพื่อศึกษาลักษณะทางคลินิกของโรค การรักษา และผลการรักษาของผู้ป่วยโรคมะเร็งก้อนทูมที่มีผลต่อการเกิดภาวะหลอดเลือดดำอุดตัน และลักษณะทางคลินิกที่เป็นไป

วิธีการวิจัย: ได้ศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยในโรคมะเร็งก้อนทูมที่ไม่รวมมะเร็งทางนรีเวชใน รพ.รามาธิบดี ที่มีภาวะหลอดเลือดดำอุดตัน ตั้งแต่ 1 มค. 2546 ถึง 28 ธค. 2550 โดยเก็บข้อมูลชนิดโรคมะเร็ง ระยะโรค การรักษา การดำเนินโรค และการเกิดภาวะหลอดเลือดดำอุดตัน ลักษณะทางคลินิค และความเสี่ยงอื่นๆ ที่เคยมีรายงานว่ามีความสัมพันธ์ร่วมด้วย รวมทั้งการใช้ยารักษาภาวะดังกล่าว และผลแทรกซ้อน

ผลการศึกษา: พบว่ามีผู้ป่วยมะเร็งในการศึกษา 178 ราย เป็นชายหญิงอย่างละเท่าๆ กัน อายุเฉลี่ย 58.77 ปี เกิดในมะเร็งปอด ลำไส้ใหญ่ เต้านม และตับกับทางเดินน้ำดี เป็นห้าอันดับแรก จากมากมาน้อย ในการศึกษานี้พบว่ามี VTE ในมะเร็งมีระยะแพร่กระจาย มีก้อนลุกลามเฉพาะที่ที่มาก ดื้อต่อการรักษา และมีการกลับเป็นซ้ำใหม่เป็นจำนวนมาก พยาธิวิทยาของชิ้นเนื้อมะเร็งที่พบมากที่สุด คือ Adenocarcinoma ร้อยละ 50 ของผู้ป่วยจะมี VTE พร้อมๆ กับการตรวจพบโรคมะเร็ง จำนวนที่เหลือจะพบภาวะหลอดเลือดดำอุดตัน หลังการตรวจพบโรคมะเร็งในเวลาเฉลี่ย 13.3 เดือน พบความสัมพันธ์ของตำแหน่งของหลอดเลือดที่ผิดปกติกับตำแหน่งก้อนทูม และการใส่ PORT implantation หลังจากมี VTE แล้ว ผู้ป่วยจะเสียชีวิตในระยะเวลาเฉลี่ย 22.3 เดือน โดยรวมพบว่าเพศหญิงจะรอดชีวิตดีกว่าผู้ชาย ($p=0.0123$) รวมทั้งชนิดของโรคมะเร็งที่มะเร็งเต้านมและมะเร็งลำไส้ใหญ่จะพบมีการรอดชีวิตดีกว่า ($p<0.001$) ผู้ป่วยที่ได้รับการรักษาหลอดเลือดดำอุดตัน หนึ่งในสามของผู้ป่วยจะมีเลือดออกผิดปกติ โดยเป็นจาก warfarin และร้อยละ 60 จะเกิดภายในหนึ่งเดือนหลังให้ยาแล้ว

สรุปการศึกษา: ผู้ป่วยที่เป็นมะเร็งที่มี VTE จะมีการพยากรณ์โรคที่ไม่ดี และพบในมะเร็งที่มีระยะแพร่กระจาย และไม่ตอบสนองต่อการรักษา อย่างไรก็ตาม การรักษา VTE ด้วย Warfarin อาจทำให้มีภาวะเลือดออกผิดปกติได้ แต่การศึกษานี้ยังมีจำนวนน้อยจึงต้องทำการศึกษาต่อไป เพื่อที่จะได้ข้อมูลที่มากขึ้น

คำสำคัญ: Venous thromboembolism, Solid cancer