RESEARCH ARTICLE

Incidence and Clinical Characteristic of Venous Thromboembolism in Gynecologic Oncology Patients attending King Chulalongkorn Memorial Hospital over a 10 Year Period

S Oranratanaphan[1]*, W Termrungruanglert[2], N Khemapech[2]

Abstract

Background: Venous thromboembolisms (VTEs) constitute a group of diseases including deep vein thrombosis (DVT) and pulmonary embolism (PE). They regarded as the second leading cause of death in cancer patients and several studies have confirmed that VTEs have a negative impact on survival and recurrent rate in both ovarian and endometrial cancer cases. The incidence of VTEs differs worldwide and depends on several risk factors including race, underlying disease, lifestyle, body weight, BMI and genetic risk factors. There is heterogeneity of DVT rates between Asian and Western countries. This study was conducted in order to evaluate the character and incidence of VTEs in gynecologic oncology patients in King Chulalongkorn Memorial Hospital over a 10 year period. Materials and Methods: A retrospective chart review was performed with VTEs defined as objective diagnosis of acute DVT or PE with typical symptoms and signs. Diagnoses were approved byan internist and/ or confirmed with imaging studies. Data from both outpatient and inpatient sessions of the affected cases from January 2004 to December 2013 were extracted. General characteristics of the patients were collected with details of the diseases, types of cancer, stage, date of diagnosis of cancer, operative data, treatment outcome, progression free survival and overall survival. Results: Thirty cases of VTEs were identified in a total 2,316 gynecologic oncology cases. The incidence of symptomatic VTEs in total gynecologic oncology patients in our institution is 1.295%. The incidence of VTEs in ovarian cancer patients in our institution was 5.9%. Duration for VTE detection ranged from 13 months before diagnosis of cancer to 33 months after diagnosis of cancer. Most of the VTE cases were detected in ovarian cancer patients (60%). The most common cell type was adenocarcinoma (moderately to poorly differentiated) which accounted for 26.7% of the cases. The second most common cell type was clear cell carcinoma with 23.3% of the cases. Thirty percent of VTE cases developed before cancer was diagnosed, 20% were diagnosed at the same time as cancer detection and fifty percent developed after cancer was diagnosed. Median disease free survival of the gynecologic oncology patients with VTE was 7.5 months. Median overall survival (OS) was 12 months. Median progession free survivals of DVT and PE groups were 11.5 and 5.5 months, respectively. OS of DVT and PE was 12.0 and 11.5 months respectively. Conclusions: The incidence of VTE in Asian countries is believed to be lower than in European or Western countries. From our retrospective review, the incidence of VTEs in all types of gynecologic oncology was 1.295%, much lower than reported in the West. The reason for the lower incidence may genetic differences. Another factor is that VTE in this review was symptomatic, which is less than asymptomatic VTE. More than half of VTEs in this study developed in ovarian cancer patients. The results are compatible with earlier reports that among gynecologic malignancies, the incidence of VTE is highest in ovarian cancer.

Keywords: Vvenous thromboembolisms - gynecologic cancer - DVT - PE - Thailand

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Introduction

Venous thromboembolism (VTE) is a group of disease including deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is considered as a major surgical complication because VTE is frequently associates with postoperative or peri-operative morbidity and mortality (Montoya et al., 2014). There is a review claimed that risk of VTE in gynecologic surgery was 17-40% and higher risk was found in gynecologic oncology surgery (Geerts et al., 2004). Moreover, VTE is regarded as the second leading cause of death in cancer patients (Donati., 1995; Heidrich et al., 2009). On the other hand, cancer is associated with 2 to 4 fold increased risk of VTE (Heit et

*Department of Obstetrics and Gynecology, [1]Thai Red Cross Society, King Chulalongkorn Memorial Hospital, [2]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand *For correspondence: dr_shina@hotmail.com*

al., 2000; Prandoni et al., 2002). Therefore, malignancy has been widely recognized as a substantial risk factor for VTE and particular types of cancer associated higher risk than usual (Rickles et al., 1983). The complexity of mechanism for pathogenesis of hypercoagulable state in malignancy was proposed. Malignancy involved a combination of thrombin generation due to binding of tissue factor with clotting intermediates, direct procoagulant activity of normal host cells in the presences of tumor, and underlying co-morbidities (Prandoni et al., 2005; Young et al., 2012). Several studies confirmed that DVT with or without PE is a common complication of malignancy especially in ovarian cancer. VTE related to malignancy is a serious life threatening event that associates with poorer outcome (Pruemer et al., 2005; Satoh et al., 2007; Peedicayil et al., 2011). Several studies confirmed that VTE had negative impact on survival and recurrent rate in both ovarian and endometrial cancer (Rodriguez et al., 2007; Sandhu et al., 2010; Diaz et al., 2013; Matsuo et al., 2013).

Risk factors of VTE in gynecologic oncology patients included age, race, pelvic surgery, previous leg edema, presence of venous varicosities, and history of VTE, long operative time, intravenous catheterization, chemotherapy administration, radiotherapy and immobilization (Clarke-Pearson et al., 1987; Ailawadi et al., 2001). In some Western countries, incidence of VTE in gynecologic oncology patients is as high as 29% (Heidrich et al., 2009). Therefore, VTE prophylaxis is recommended for gynecologic oncology patients who required surgical intervention. Despite of using thromboprophylaxis, some patients still developed VTE after discharge from the hospital. Some data claimed that one third of the postoperative VTE developed after discharge from the hospital because VTE prophylaxis is given to most cancer patients only during hospitalization and discontinuation after discharge (Merkow et al., 2011). On the other hand, using anticoagulant can cause some complication. Some research claimed that risk of major bleeding from anticoagulant was more common in cancer patients. Major bleeding occur 12.4% (95%CI6.5-18.2) of cancer patients and 4.9% (95%CI 2.5-7.4) in non cancer patients (HR 2.2 [05%CI 1.2-4.1]) (Prandoni et al., 2002; Streiff, 2015).Therefore, it still has some conflict among expert recommendation and routine practice on the optimal duration of VTE prophylaxis. The decision for duration of thromboprophylaxis should be taking by balancing the risk of VTE and risk of bleeding. Factors that should be considered for making the decision are the incidence and burden of the VTE. Moreover, incidence of VTE is difference worldwide depends on several risk factors including race, underlying disease, life style, weight, BMI and genetic risk factor (Rodriguez et al., 2011). Rodriguez AO et al confirmed that there were racial differences in both rate of VTE and risk of death in women with a diagnosis of uterine cancer in their study (Martino et al., 2007; Rodriguez et al., 2011). Incidence of cancer and details of common cell type are also different between races. There were some studies confirmed the difference in common cell type in ovarian tumor in Thai patients comparing to worldwide incidence (Oranratanapan et al., 2013; Kunpalin et al., 2014). There was a study about VTE in orthopedic surgery in Asian patients found that VTE risk for Asian patients may be being lower than western reports (Kanchanabat et al., 2011). Moreover, there is heterogeneity of DVT rate in Asian countries. For example, incidence of VTE in orthopedic surgery patient in South East Asia is 4.4%, Korean 2.8% and Indian 1.5%.

Therefore, the incidence of VTE in Thai gynecologic oncology patients may different from worldwide incidence. This study was conducted in order to evaluate the character and incidence of VTE in gynecologic oncology patients in King Chulalongkorn Memorial Hospital in 10 years duration.

Materials and Methods

After Ethical Committee of Faculty of Medicine Chulalongkorn University approved this protocol, the study was conducted. Retrospective chart review was performed. All of the charts of gynecologic oncology patients who were treated in King Chulalongkorn Memorial Hospital during January 2004 and December 2013 were reviewed. Total 2,316 cases of gynecologic oncology were searched for venous thromboembolism, deep vein thrombosis and pulmonary embolism by ICD 9 and ICD 10 coding. VTE including DVT and PE was defined as objective diagnosis when symptoms and signs of acute VTE occurred. The diagnosis was approved by internist in the same admission that VTE episode occurred and/ or confirmed with investigation such as venography, compression duplex ultrasono-venography or computed tomographic venography. Gynecologic oncology cases included ovarian cancer, uterine cancer, cervical cancer, fallopian tube cancer and peritoneal cancer. Peritoneal and fallopian tube cancers were counted as ovarian cancer because of the similarity of natural history and treatment.

From total 2,316 gynecologic oncology cases, 30 cases of VTE were identified. Data both from outpatient and inpatient sessions of those affected cases were extracted. The inclusion criteria were gynecologic oncologic patients who developed VTE before, during or after the diagnosis of malignancy. General characteristics of the patients such as age, race, weight, height, BMI, underlying diseases and current medication usage were collected. According to details of gynecologic oncology disease, types of cancer, stage, date of diagnosis of cancer, treatment options, operative records, operative time, estimated blood loss, operative complication, operative result, optimal of surgery, treatment outcome, progression free survival and overall survival were collected. Progression free survival (PFS) was defined as time from completion of primary treatment to time of detection of recurrence. In case that recurrence was not detected, PFS was calculated to the date of death or last follow up visit. Overall survival (OS) was defined as time from the date of diagnosis of the disease to the date of death. If the patients still survived within the study period, OS was calculated to the date of last follow up visit. In the aspect of VTE, date of diagnosis of VTE, investigation, timing related to the date of diagnosis of cancer and treatments of VTE were also recorded.

SPSS version 17.0 was sued to calculate and analyze

the data. General characteristics of the patients were analyzed with mean, mode, median and percentage as suitable. Independent T test were used to calculate parametric data. Chi-square and other non-parametric test were used to calculate and analyzed non parametric data.

Results

In 10 years duration (from January 2004 to December 2013), total 2,316 gynecologic oncology patients' history and diagnosis were searched. We found 30 cases of VTE in gynecologic oncology patients. The incidence of symptomatic VTE in total gynecologic oncology patients in our institution is 1.295%. In case that we calculated only ovarian cancer cases, the incidence of VTE in ovarian cancer patients in our institution is 5.9%. Mean age of the patient was56.4 years. Mean BMI was 23.02 kg/m^2. Most of the patients were Thai (29 subjects). Only 1 patient was Chinese. Nearly half of the patients had underlying disease (14 from 30 cases). The most common underlying disease was hypertension. General characteristics of the patients were demonstrated in Table 1.

Duration for VTE detection ranged from 13 months before diagnosis of cancer to 33 months after diagnosis of cancer. Most of the VTE cases were detected in ovarian cancer patients (60%), 20% of the cases were uterine cancer. The most common cell type was adenocarcinoma (moderately to poorly differentiate) which included 26.67% of the cases. The second most common cell type was clear cell which was 23.33% of the cases. According to the duration of VTE development, 30% of VTE cases developed before cancer was diagnosed, 20% of VTE was diagnosed at the same time of cancer detection and half of them (50%) of VTE developed after cancer was diagnosed. Median time of VTE diagnosis was within 1 month after diagnosis of cancer. Most of VTE cases were confirmed with duplex ultrasonogram or computed tomographic venography (96.66%). Most common treatment for VTE was low molecular weight heparin (83.33%), the rest of the patients received oral anticoagulant as a treatment. Most of VTE cases were diagnosed at the first diagnosis of cancer (73.33%) One fourth of the patients developed VTE when the cancer recurred. More than half of the patients received surgical treatment (70%) and 30% of the patients received non surgical treatment. In surgical cases (21 cases), 14 cases were primary surgery and 7 cases were interval debulking surgery. Half of the patients (10 from 21) achieved complete cytoreduction. Only 4 cases from total 21 cases were suboptimal resection. From the review, no thromboprophylaxis was used before the surgery except in the cases that VTE was diagnosed before the surgery. Mean operative time was 150.94 min (SD 55.98, range 50-300 min). Mean blood loss was 716.67 ml (SD 596.32, range 100-2000). Details of VTE and cancer were shown in Table 2.

For non surgical and adjuvant treatment, chemotherapy was administered in 14 (46.67%) patients. The most common chemotherapeutic regimen was carboplatin and paclitaxel. Radiotherapy was given to 10 (33.33%) patients. According to the survival outcome, 6 from 30 patients died in the first admission period. More than half of those patients had both DVT and PE (4 from 6), one patient had DVT and another one patient had PE. From 24 patients who survived from the first diagnosis of VTE, cancer recurrence was detected in 15 of them (62.5%). Until the end of the study 23 from 30 patients died. Seven patients (23.33%) are still alive. Five of the survival patients were ovarian cancer cases and 2 of the survivals were uterine cancer patients. Median DFS of

Table 1. General Characteristic of the Patients

Characteristics	Mean (SD)
Age (years)	56.4 (9.8)
Height (cm)	152.5 (5.4)
Weight (kg)	54.0 (12.6)
BMI	23.0 (4.8)

Table 2. VTE and Cancer Details

Character	N (percentage) (total N=30)
Carcinoma	
Ovarian	18 (60.0)
Uterine	6 (20.0)
Cervix	5 (16.7)
vulva	1 (3.3)
Cell type	
Adenocarcinoma	8 (26.7)
Clear cell	7 (23.3)
Endometrioid	4 (13.3)
Squamous	4 (13.3)
Sarcoma	3 (10.0)
Other	1 (3.3)
Duration of VTE diagnosis	
Before diagnosis of cancer	9 (30.0)
At the same moment	6 (20.0)
After diagnosis of cancer	15 (50.0)
Type of VTE	
DVT	11 (36.7)
PE	5 (16.7)
DVT and PE	14 (46.7)
VTE Diagnostic method	
Clinical	1 (3.3)
Duplex ultrasonogram	13 (43.3)
CT angiogram with or without ultrasound	16 (53.3)
VTE treatment	
LMWH	25 (83.3)
Oral anticoagulant	5 (16.7)
Cancer treatment	
Surgical treatment	21 (70.0)
Primary surgery	12 /21 (66.7)
Interval debulking	7/21 (33.3)
Non surgical treatment	9 (30.0)
Surgical outcome (N=21)	
Complete cytoreduction (no residual)	10 (47.5)
Optimal cytoreduction (residual <1 cm)	6 (28.6)
Suboptimal cytoreduction	4 (19.1)
Missing data	1 (4.8)

Table 3. Comparing PFS and OS between DVT and PE

	All cases (N=30)	DVT (N=11)	PE (N=19)	P value
Progression free survival	7.5	11.5	5.5	0.515
Overall survival	12.0	12.0	11.5	0.297

all VTE cases was 7.5 months (range 0-116 months). Median overall survival was 12 months (0-116 months). We separate VTE into DVT group and PE group. In PE group, it included pure PE and PE accompany with DVT. Median PFS of DVT and PE group were 11.5 and 5.5 months respectively. OS was 12.0 and 11.5 months respectively. Comparing OS and PFS between DVT and PE (including PE and PE with DVT) did not demonstrate statistic significance in difference. Median OS and PFS of PE and DVT were demonstrated in Table 3.

Discussion

VTE is now recognized that is associated with cancer. Moreover, VTE in gynecologic oncology patients is confirmed to have negative effect on progression free survival and overall survival. Furthermore, VTE is the second cause of death in gynecologic oncology patients (Heidrich et al., 2009). Among western women undergoing gynecologic surgery without thromboprophylaxis, the risk of DVT ranges from 17-40% (Geerts et al., 2004). However, VTE is the most common cause of preventable deaths in hospitalized patients in the United State (Heit et al., 2002). Therefore, VTE prophylaxis before surgery is now recommended by several committees (Committee on Practice Bulletins-Gynecology, 2007; Lyman et al., 2013; Ramirez et al., 2013).

On the other hands, the incidence of VTE varies worldwide according to the differences of genetic predisposition. The incidence of VTE in Asian countries is believed to be lower than in European or Western countries. From our retrospective review, incidence of VTE in all types of gynecologic oncology was 1.295%. That incidence is much lower than Western countries' incidence. Moreover, even subgroup analysis on ovarian cancer was done; the incidence of VTE was 5.9%. That number is still lower than European or western's data. The reasons for the lower incidence may from the genetic differences and VTE in this review was symptomatic VTE which was much lower than asymptomatic VTE. All of the subjects in this study was symptomatic VTE and confirmed the diagnosis by imaging techniques such as duplex ultrasonogram and CT angiogram. Therefore, the incidence of VTE is less than other published studies that included both symptomatic and asymptomatic VTE.

From this study, all of the subjects did not receive VTE prophylaxis before the surgery except the cases that VTE was diagnosed before surgery. Therefore, this incidence of VTE should be the real incidence of VTE because it is not confounded by thromboprophylaxis administration. More than half of VTE cases in this study developed in ovarian cancer patients. It is compatible with several studies that among gynecologic malignancy, the incidence of VTE is highest in ovarian cancer. While, three fourth of the patients developed VTE in primary diagnosis of cancer period; one fourth developed VTE at the cancer recurrence episode. Therefore, it should be noticed that if VTE developed during follow up visits in cancer survival patients, recurrence should be suspected. According to cell type of cancer, half of the VTE cases are adenocarcinoma and clear cell carcinoma. From the previous study confirmed that VTE is highly associated with severe and aggressive histological subtype (Diaz et al., 2013). Ovarian clear cell carcinoma is associated with a higher risk of VTE development than other malignant cell types (Matsuura et al., 2007; Carmen et al., 2012). Cancer related VTE might not only be a surrogate marker for aggressiveness of the tumor, but that thrombosis itself might directly or indirectly modify tumor biology contributing the poorer outcomes (Zwicker et al., 2009; Berg et al., 2012).

PFS and OS between DVT and PE in this study was no statistically difference. It may result from the number of subjects in this study is too small to detect the difference. Therefore, next study with more subjects may be required.

The limitation of this study was the study design. This retrospective study has many limitations such as data missing and incomplete of data. For further investigation or research prospective design can reduce these limitations.

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