



Evaluation of Drug Regimens Used for the Prophylaxis of Thromboembolic Events in a Referral Cancer Center in North of Iran

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ABSTRACT

Background: Venous thromboembolism (VTE) is a major cause of mortality among cancer patients. The aim of this study was to evaluate drug regimens used for the prophylaxis of thromboembolic events in cancer patients.

Methods: A retrospective study was conducted using medical records of patients hospitalized from March 2012 to March 2014 at Cancer Division of a tertiary university-affiliated hospital in North of Iran. The risk factors of patients regarding need of venous thromboembolic (VTE) prophylaxis were recognized and dosage and duration of thromboembolic prophylactic agents were evaluated according to the National Comprehensive Cancer Network (NCCN) 2012 guidelines. Statistical analysis was performed using SPSS v.23.

Results: Of a total of 1160 medical records, VTE prophylaxis regimens of 186 patients were evaluated. In 18 (13.1%) and 15 (10.9%) of patients, administrations were compatible with NCCN guidelines with respect to the "type of drug" and "dosage", respectively. Only in 7 (5.1%) of patient administrations were compatible with respect to the "duration of thromboembolic prophylaxis regimen". Forty patients (21.7%) had relative contraindications for thromboembolic prophylaxis and 7 (3.8%) patients had absolute contraindication. In 32 (80%) of 40 patients with relative contraindications and only in 1 (14.3%) of 7 patients with absolute contraindications, physicians' orders were compatible with NCCN guidelines.

Conclusion: The rate of concordance of the VTE prophylaxis with recommendations provided by NCCN was very poor. This study emphasizes the need of a multidisciplinary action to improve the VTE prophylaxis in cancer patients.

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Introduction

Venous thromboembolism (VTE) is relatively prevalent

and is also a major cause of mortality among cancer patients. Symptoms usually develop gradually and silently in VTE. Cancer patients experience a threefold increase in morbidity and mortality due to thromboembolic events compared to non-cancer patients (1). The incident risk of thromboembolic events is 2 to 7 fold higher in cancer patients relative to non- cancer patients (2). Risk factors

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of happening deep vein thrombosis (DVT) are usually present in cancer patients (3). These risk factors could be classified into three groups: factors related to the patient, factors related to the disease (in this case cancer) and factors related to the treatment. For estimating the universal risk of a thromboembolic event all risk factors should be considered altogether and it is impossible to conclude about to happen thromboembolic event by regarding single risk factors independently (4). Risk factors related to patients include: hospitalization, presence of other medical problems like infections and long term immobility (5). Immobility which itself could result in venous blood stasis has been recognized as a risk factor for DVT from long time ago. In cancer patients, functional status is frequently used in clinical assessments (6). Infections are known to be an important risk factor for the occurrence of thromboembolic events in cancer and non-cancer patients (7). Cancer patients who have undergone surgery, have been hospitalized and were immobile for more than 3 days frequently experience thromboembolic events (8). Advanced age is usually associated with increased risk of thromboembolic events (9). Ages greater than 65 in hospitalized patients were proportionately associated with increased risk of thromboembolic events. In addition, in surgical circumstances, ages greater than 60 increase the probability of a DVT occurrence (10).

Chemotherapy is the most important treatment related factors in the DVT occurrence in cancer patients. Large population-based studies showed a 2 to 6 fold increase in incidence of DVT in patients receiving chemotherapy (11). Access to central veins by means of devices like central venous catheters is frequently used for infusion of chemotherapeutic agents. Prevalence of catheter related DVT in adult patients estimated to be between 0.3% to 8.2% and its prevalence based on venography estimated to be between 27 to 66 percent (12).

The aim of this study was to assess the risk of DVT development in our cancer patients and also the concordance of practice of VTE prophylaxis with recommendations of NCCN guidelines.

Methods

This retrospective study was performed using medical records of patients hospitalized in Imam Khomeini Hospital, from March 2012 to March 2014. Imam Khomeini hospital is a tertiary care university-affiliated hospital located in Sari, North of Iran. All cancer patients who admitted at the hospital for receiving their chemotherapy regimen or for any other reason were eligible to include in the study.

Of a total of 1160 patients who had been admitted, 232 (20%) were randomly recruited in the study and the required demographic and clinical data were extracted from their medical records. Sex, age, type of cancer, duration of hospitalization, wards in which patients admitted,

any contraindication for receiving thromboprophylaxis, type of drug regimens used, dosage and duration of administration were among the variables studied. As some of the medical records of the patients lacked some data needed for completion of data gathering forms, finally records of 186 patients were used in the analysis. Type of the drug regimen used for thromboprophylaxis in these patients, dosage and duration of administration were evaluated according to the NCCN guidelines version I, 2012. Based on different recommendations in NCCN guidelines, patients were classified into three groups including "Non multiple myeloma patients without surgery", "myeloma patients" and "Non multiple myeloma patients undergone surgery". The risk factors of patients regarding the need of venous thromboembolic (VTE) prophylaxis were recognized and the dosage and duration of thromboembolic prophylactic agents were evaluated according to the NCCN guidelines. According to NCCN guidelines all cancer patients admitted at the hospital should receive thromboembolic prophylaxis during their admission, unless there is a contraindication for use of anticoagulant agents. Several conditions considered as relative or absolute contraindications for thromboembolic prophylaxis. Absolute contraindications for anticoagulant drugs include: acute bleeding in CNS and spinal injuries with high risk of bleeding, massive active bleeding (requiring more than 2 units of whole blood in 24 hours), recent spinal anesthesia or lumbar puncture. Determining relative contraindications require careful evaluation of potential harms and benefits of using these agents. Relative contraindications include: acute or chronic bleedings lasting for more than 48 hours, extended surgeries with high risk of bleeding, high risk of falling down and head injury, thrombocytopenia (less than 50000 plts in microliter), severe diseases involving platelets such as uremia, myelodysplastic syndrome and high risk of systemic thrombotic problems which could be find out by measurement of prothrombine time (PT) and activated partial thromboplastine time (aPTT). As a general rule NCCN guidelines emphasize on frequent evaluation of potential harms and benefits of using anticoagulant agents in patients who have any risk for bleeding.

Statistical analysis was performed using SPSS v.23. Descriptive statistics were used to describe the basic and clinical features of the patients. Categorical variables were compared using the chi-square or Fisher.

Results

Of a total of 186 patients recruited in this study 101 were males and 85 were females. Mean age of the patients were 56 ± 17 years. About 80 percent of patients was in the age distribution of 40 to 80 years old. The most prevalent cancer was colorectal cancer (26 patients; 14%) followed by gastric cancer (24 patients; 12.9%) and lymphoma (20 patients; 10.8%). Most of cancer patients (118 patients;

Table 1. Demographic and clinical data of patients.

Age (years); mean±SD	56±17
Age distribution; n (%)	
< 20	9 (4.8)
21-39	23 (12.4)
40-59	73 (39.2)
60-79	73 (39.2)
≥ 80	8 (4.3)
Sex	
Male (%)	101 (54.3)
Female (%)	85 (45.7)
Type of Cancer; n (%)	
Colorectal	26 (14)
Gastric	24 (12.9)
Leukemia/lymphoma	20 (10.8)
Lung	17 (9.2)
Breast	11 (5.9)
Bladder	11 (5.9)
Multiple Myeloma	4 (2.2)
Other	73 (39.2)
Surgery; n (%)	
Yes	68 (36.6)
No	118 (63.4)
VTE used; n (%)	
Yes	42 (22.6)
No	144 (77.4)
Days of hospital stay	
Mean	9.2
SD	6.8
Min	1
Max	33
Days On anticoagulants	
Mean	1.2
SD	3.2
Min	0
Max	30

63.4 %) were not undergone surgery. VTE performed in 42 (22.6%) of patients. Mean duration of hospital stay was 9.2 days and mean duration of receiving anticoagulants was 1.2 days (Table 1).

Forty patients (21.5%) patients had relative contraindications and 7 patients (3.8%) had absolute contraindications. Of a total of 136 patients (three missed data) without any contraindication, in 13.1% of patients the administered drug regimens were compatible with NCCN

guidelines with respect to the type of drug, in 10.9% the administered drug were compatible with respect to dosages and only in 5.1% of patients the administered drug was compatible with respect to duration of administration (Table 2).

As noted above, 47 patients had a relative or absolute contraindication of using anticoagulants. One patient of 7 patients with absolute contraindication for thromboprophylaxis (14.3%) and 8 patients of 40 patients

Table 2. Compatibility of thromboprophylactic regimens with NCCN guidelines in patients without any contraindications of VTE prophylaxis (N=136).

	Number	Percent
Drug used for thromboprophylaxis		
Compatible	18	13.1
Not Compatible	118	86.1
Dose of drug used for thromboprophylaxis		
Compatible	15	10.9
Not Compatible	121	89.1
Duration of drug used for thromboprophylaxis		
Compatible	7	5.1
Not Compatible	129	94.2

with relative contraindication for thromboprophylaxis (20%), received thromboprophylactic drugs. Data of mean hospital stay and days on anticoagulants have been presented in Table 3. The mean days of receiving anticoagulants were 1.14 and 0.98 in patients with a relative or absolute contraindication, respectively.

The risk of development of thrombosis in Non-myeloma patients who had not a surgery in the process of their treatment was determined according to risk stratifying approach introduced by Khorana et al., (13). The risk determines according to variables, including location of the cancer, platelet count, white blood cell and hemoglobin levels before chemotherapy.

Patients with a score of 3 will be classified as a high risk group and patients with a score of 1 or 2 will be considered moderate risk. A score of 0 classifies the patient as a low risk group.

Considering the risk stratifying of the thrombosis, 102 and 84 patients classified as high risk and low risk group, respectively. High risk group had to receive thromboprophylaxis (Table 5).

Indeed, only 42 patients received VTE prophylaxis in our study, of them 9 patients had a relative or absolute contraindication of using anticoagulants.

Discussion

In the present study, we tried to evaluate the usage of thromboprophylactic drugs in cancer patients. In general, administration and usage of these drugs in this group of patients were not appreciably compatible with NCCN guidelines. According to previous studies, cancer patients are at high risk for life-threatening thromboembolic events. Results of a retrospective study performed by Khorana and colleagues on 66106 neutropenic cancer patients showed that 1.12 to 7.2 percent of these patients, according to their cancer type, experienced DVT at their first hospital admission. Inpatient mortality rate during 8-years after starting the study period was more than 3.8% and patients who experienced DVT had a higher mortality rate than those who did not (9). Rogers and colleagues published a case-control study performed on 16781 patients whose ages were 52 years or older and were hospitalized because of DVT. They introduced infection, using an erythropoiesis stimulating agent, blood transfusion, extended surgeries, fractures, immobility and chemotherapy as major risk factors responsible for thromboembolic events (7). Chemotherapy itself increases the risk of VTE, as it has been demonstrated by Numico et al., on NSCLC patients treated with cisplatin and

Table 3. Characteristics of patients with relative or absolute contraindications of anticoagulant use.

	Relative Contraindication	Absolute Contraindication
Number	40	7
Receive of Anticoagulant; n (%)		
Yes	8 (20)	1 (14.3)
No	32 (80)	6 (85.7)
Days of hospital stay	9.1±6.8	14.33±9.56
Days on anticoagulant	1.14±3.02	0.98±2.2

Table 4. Khorana risk stratification of non-myeloma patients who did not have a surgery intervention.

	Number	Percent
Location of Cancer		
High Risk	24	21.1
Low Risk	46	40.4
Without Risk	44	38.6
Platelets before Chemotherapy		
> 350000 /mm ³	16	14
< 350000 /mm ³	98	86
WBC before Chemotherapy		
> 11000/mm ³	26	26
< 11000/mm ³	88	88
Hb before Chemotherapy		
< 10 g/dl	63	55.3
> 10 g/dl	51	44.7
Khorana Score		
3 (High Risk)	30	26.3
1-2 (Moderate Risk)	62	54.4
0 (Low Risk)	22	19.3

Hb: Hemoglobin; WBC: White Blood Cells.

gemcitabine (6).

Type of cancer also plays an important role in the risk of thromboembolic events. Based on a study conducted by Blom et al., cancers that accompany a high risk of DVT occurrence include: colon, kidney, bladder, lung, ovary, uterus and testis (14). In the present study, we tried to assess the risk of DVT in different cancer populations, including patients with different solid tumors with and without having surgery as a treatment modality during their course of treatment and also hematopoietic malignancies (e.g. multiple myeloma, leukemia and lymphoma). Cancers with highest probability of DVT occurrence in our study were colorectal cancers (26 patients, 14%) and gastric cancer (24 patients, 12.9%). Moreover we had 8 cases of pancreatic cancer patients (4.3%), 5 cases of brain cancers (2.7%) and 4 cases of

multiple myeloma (2.2%), all have been recognized as high risk malignancies regarding VTE.

Treatment related factors could also increase risk of thromboembolic events in cancer patients. For example Heit et al., showed that patients who underwent surgery or patients that did not have a surgery but admitted at a hospital or nursing home are 22 and 8 time more probable to experience a DVT respectively (15). In our study, 68 cases of included patients (40 males and 28 females, 36.6%). Among patients that had undergone surgery, 67 patients had experienced an anesthetic procedure of more than 2 hours that is a risk factor for developing DVT during hospitalization.

According to NCCN guidelines all cancer patients who are admitted at the hospital require thromboprophylaxis during their admission, unless there is contraindication of

Table 5. Risk stratification of all patients according to NCCN classification for determining risk of thrombosis.

	Non multiple myeloma patients without surgery	Multiple Myeloma	Non multiple myeloma patients undergone surgery	Total
Risk of thrombosis				
High Risk (need of thromboprophylaxis)	30	4	68	102
Low Risk (no need of thromboprophylaxis)	84	0	0	84

use of anticoagulants. Most of our patients (136 of 186; 73%) did not have any contraindications and should have received anticoagulants according to NCCN guideline. Indeed the rate of meeting the criteria of NCCN was very poor in our setting, as 13%, 10.9% and 5.1% of our patients received compatible drug, dose and duration of anticoagulant according to NCCN recommendations. Considering the importance of VTE especially in cancer patients with multiple predisposing factors for development of VTE, it is necessary to emphasize that high risk patients should be recognized and all aspects of VTE prophylaxis (e.g., type of agent, dosage and duration of administration) should be performed as recommended by the standard guideline such as NCCN. The results of this study demonstrate need of re-evaluating our practice regarding the VTE prophylaxis and taking actions for management of errors observed in this area.

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