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Abstract:

Introduction:

After 6 months, little is known about the optimal anticoagulant strategy for an acute episode of VTE in cancer patients.

Aims, objectives and methods:

The objective was to determine the risk of recurrent VTE and anticoagulant-related bleeding at 6 months of follow-up and after 6 months, in cancer patients who received tinzaparin during at least 3 months for an acute episode of VTE. We conducted a multicenter retrospective cohort study from January 2004 to March 2011.

Results:

Two hundred fifty patients were included. Stopping anticoagulation before 6 months in patients considered at low risk by physicians (i.e.; patients who had prior cancer surgery) and for another reason than bleeding or death was the only factor associated with a significant increased risk of recurrent VTE (OR 7.2 95%CI, 2.0-25.7; p=0.002). The type of anticoagulation did not influence the risk of recurrent VTE. We found a trend towards an increased risk of recurrent VTE when anticoagulation was stopped because of major bleeding while on anticoagulant therapy and patients with metastatic cancer (OR 2.3, 95%CI, 0.9-5.4; p=0.07; and OR 1.8 95%CI, 1.0-3.3; p=0.07; respectively). No factors were found to increase the risk of major bleeding at 6 months and after. The overall mortality was 42.8%.

Conclusions:

The risk of recurrent VTE was mainly related to early discontinuation of anticoagulation in patients considered at low risk of recurrence (after surgery). When the anticoagulation was stopped before the sixth month, the risk was eight fold higher. After 6 month, the risks of recurrent VTE, major bleeding and death were similar in patients with either VKA or tinzaparin when patient was treated according to the guidelines.

Keywords:

Venous thromboembolism, cancer, pulmonary embolism, anticoagulation

Introduction:

The strength of the association between the presence of an active cancer and the occurrence of a venous thromboembolism (VTE) has been demonstrated. In epidemiological studies [1-4], cancer patients have not only an increased risk of developing a first episode of VTE, but also an increased risk of VTE recurrence, even while on anticoagulant therapy. Moreover, the risk of anticoagulant-related bleeding is increased in those patients [4]. Thus, treatment of VTE in cancer patients remains a challenging issue.

During the past decade, a major finding was the demonstration in three open label randomized trials [5-7] that low-molecular weight heparins (LMWH) use, administered at therapeutic dose during 3 to 6 months in cancer patients with acute VTE, was associated with a 50% relative risk reduction of recurrent VTE in comparison to vitamin K antagonists (VKA) use. Based on these consistent observations, LMWH are currently recommended during the first 3 to 6 months of VTE in most patients with active cancer [8-12].

A convincing demonstration has been provided by the *CLOT* trial [5] that compared dalteparin to warfarine during the first 6 months following an acute VTE in 600 patients with an active cancer. The two other studies made use of enoxaparin or tinzaparin versus VKA: evidence in favor of the use of these particular LMWH appears lower, due to study limitations. In the study comparing enoxaparin to VKA [7], only a trend in favor of enoxaparin use was observed for the prevention of recurrent VTE at 6 months. In the study comparing tinzaparin to VKA [6] in 200 patients with an acute DVT, patients were only followed up for the first three months. None of these trials followed up patients after 6 months and little is known about the optimal anticoagulant strategy after this period. However, beyond the first 3 to 6 months, extended anticoagulation should be considered for an indefinite period or until the cancer is cured [12].

In the present study, we first aimed to appraise the risk of recurrent VTE and the risk of anticoagulant-related bleeding at 6 months of follow-up, in cancer patients who were prescribed tinzaparin (the most frequent LMWH used in France during the study period because of its ease of use – one dosage, one injection-) for at least 3 months for an acute episode of symptomatic VTE. The secondary objectives were to evaluate the risk of recurrent VTE and bleeding after 6 months, while on tinzaparin or not, and to identify risk factors that were associated with an increased frequency of one or both endpoints

.

Materials and methods:

Study design and Patients

We conducted a retrospective cohort study from January, 1st 2004 to March, 31 2011 in two tertiary care hospitals.

Population

Patients were eligible if they had: (i) a solid or hematological malignancy which was active and under treatment, or in remission for less than two years; and (ii) a symptomatic VTE (PE or DVT) objectively diagnosed; and (iii), if a tinzaparin treatment after the first ten days of anticoagulation was planned for at least three months. Non inclusion criteria were: age < 18 years old, cancer in remission (disease-free or treatment for more than 2 years), another anticoagulant than tinzaparin used for long term, unsuspected VTE (e.g., asymptomatic VTE discovered on imaging), another disease than VTE treated by anticoagulant. The study was approved by the ethical committee of Brest University Hospital.

Definitions

Symptomatic VTE was defined by the presence of a proximal DVT and/or PE. The diagnosis of proximal DVT was assessed using legs ultrasound (presence of a non compression of a proximal vein [13] with or without totally implantable venous access related thrombosis); PE was diagnosed on V/Q lung scan (high PIOPED probability) associated with a high clinical pre-test probability or on spiral CT lung scan (multisegmental or more proximal pulmonary arteries) with symptoms. Major risks factors of VTE included prolonged immobilization (over 3 days) and surgery or trauma in the past three months. Minor risk factors included pregnancy, travel > 4 hours within eight days, hormonal therapy, thrombophilia, congenital or acquired, and tumor compression.

Duration of follow up and Data collection

At both centers, patients were identified from the hospital databases, with the following diagnostic codes (International Classification of Diseases version 10 - ICD-10): “Pulmonary Embolism” (I26*) or “Phlebitis (I80*)” and “Neoplasm” (C00-C97/D37-D48). All retrieved medicals records were reviewed for potential inclusion.

For each eligible patient, the observation period started at the time of VTE diagnosis and ended: (i) in the event of death, (ii) in the case of VTE recurrence or bleeding event occurrence, or (iii), if alive, at the date of the last news. The following data were extracted, using a standardized data form: age, sex, risk factors for VTE, medical history, medical VTE history, tumor characteristics (site, stage, histology, evolution, treatment in the last three months), performance status, and VTE characteristics.

Outcomes

Primary outcomes consisted in recurrent VTE and major bleeding at six months. Secondary outcomes consisted in recurrent VTE and major bleeding after six months, and death.

Recurrent VTE was assessed on the basis of the following criteria [13, 14]: recurrent DVT diagnosed if a previously compressible venous segment could no longer be compressed on ultrasonography. An extension of the thrombus was required if the results were abnormal on previous testing; recurrent PE was defined by the presence of new or enlarged areas of segmental perfusion defects with ventilation-perfusion mismatch at V/Q lung scan, or the presence of new filing defects in the pulmonary vasculature at spiral CT lung scan, or a recurrent DVT with respiratory symptoms, or evidence of fresh pulmonary embolism at autopsy. All VTE recurrences were reviewed by two authors (ELS, OS).

Major bleeding was defined according to the ISTH definition [15]: bleeding associated with death or occurring at a critical site (intracranial, intraspinal, intraocular, retroperitoneal or pericardial area), need for a transfusion of at least 2 units of blood, drop of hemoglobin of at least to 2.0g per deciliter.

Statistical analysis

Continuous variables are presented as means ± standard deviation or as medians (and 25^{th} to 75^{th} percentile range) when not normally distributed. Categorical variables are presented as numbers and percentages. Comparisons between groups were performed by univariate analyses. For continuous variables, Student't-test was used for normally distributed variables and Wilcoxon test for non-normally distributed variables. The chi-square test or Fisher test were used for categorical variables. Univariate analyses included surgery, VTE with ANTICOAGULATION preventive or curative, personal history of VTE, major and minor risk factor, VTE type, localization, histology of cancer, sex, age, staging, cancer treatment, main co-morbidities and center. Then, survival curves were computed using the Kaplan Meier

method; the effect of each variable on the risk of recurrent VTE or bleeding risk was calculated using the log Rank Test. A multivariate analysis was performed, keeping variables with a *P*-value of less than 0.2 in univariate analysis, by use of a multivariate logistic model with stepwise variable selection, to indentify factors independently associated with recurrent VTE or major bleeding.

Results

Patient's characteristics

Out of 869 patients identified through hospital databases, 619 patients were ineligible, due to an unsuspected VTE (216 patients), another anticoagulant than tinzaparin used for long term (310 patients), or another disease than VTE treated by anticoagulant (93 patients). Thus, we included 250 patients in the present cohort. Patient's characteristics are summarized in table one.

The median length of follow-up was 396 days (range 1-2678 days), for a total of 39.5 months per patients. Median duration of tinzaparin treatment was 198 days (range 1-2405 days). Anticoagulation was discontinued in 30.6% because of death, in 6% because of a major bleeding occurrence and in 15.3% because of the physician's choice. Treatment options after VTE recurrence were: tinzaparin (30.4%), VKA (21%), vena cava filter (13%), unfractionated heparin (13%). Most of VTE recurrence occurred in lung cancer patients (40%).

Primary outcomes (Table 2)

VTE recurrence at six months

Recurrent VTE occurred in 26 patients (10.4%) at six months. Main characteristics of those patients are summarized in Table 3. A reversible major risk factor (mainly surgery) was observed in 10 patients with recurrent VTE (22%). Sixty eight percent of patients received a cancer treatment in the past three months (mainly chemotherapy). Among the tested variables in univariate analysis, only stopping anticoagulation for another reason than bleeding or death was associated with a significant increase in recurrence (OR: 8.8, 95% CI, 3.3-23.6, p<0.001). This result remained significant in multivariate analysis including localization, histology, metastasis, surgery (OR: 7.2, 95% CI, 2.0-25.7, p=0.002).

Bleeding events at six months

Fourteen patients had majors bleeding events at six months. All these patients were treated with tinzaparin. Most of these events occurred during the first three months and most were digestive bleedings. In univariate and multivariate analyses, we cannot identified risk factors (including in particular switch to VKA, age, radiotherapy) associated with an increase or decrease in the bleeding risk.

Secondary Outcomes

VTE recurrence after six months

Recurrent VTE occurred in 20 patients (8%) after six months. Discontinuation of anticoagulation or switch with VKA did not interfere with the recurrence rate.

In univariate analysis, only some cancer localizations were associated with a significant increase in recurrence risk after six months: lung, kidney and pelvis (mainly sarcoma). In multivariate analysis (including duration of treatment, metastasis, major bleeding, histology and cancer localization), none variable was independently associated to the risk of VTE recurrence after 6 months. However, major bleeding (OR 2.25, IC 95%, 0.94-

5.38 p=0.07) and metastasis stage (OR 1.77 IC 0.96-3.25 p=0.07) were the only factors that might interfere with the rate of recurrence, although not achieving a significant level.

Major bleeding events after six months

Major bleeding occurred in 4 patients (1.6%). Among them, one was on tinzaparin, and the three remaining patients received VKA. In univariate and multivariate analyses, age, radiotherapy, comorbidities and histology did not interfere with the major bleeding risk. .

Deaths

There were 108 deaths (43.2%) during the follow-up, in 71 patients (28.4%) while on tinzaparin). Most of deaths occurred during the three first months of the observation period. Death was linked to cancer progression in 74 patients (29.6%), to a fatal bleeding event while on tinzaparin in three patients (1.2%) and to a fatal recurrent PE in nine patients (3.6%) (One while on tinzaparin, eight without anticoagulant therapy).

Discussion

Most of VTE recurrences and major bleeding events occurred during the first six months after the initial VTE episode. There are early events: half occurred during the first three months. Interestingly, the risk of recurrent VTE was found to be increased in patients considered at low risk of recurrence (i.e VTE witch was provoked by a major transient risk factor such as surgery) when anticoagulation (whether tinzaparin or VKA) was stopped prior to 6 months. After the first six months, the risk didn't change. None risk factor (like metastatic disease) impacted the recurrent risk: probably because of prolonged treatment in this population (>6 months).

The recurrent VTE rate at 6 months in our study is similar of the main clinical trials. In the CLOT study [5], during the six-month study period, 27 of 336 (8%) patients in the dalteparin group had symptomatic recurrent VTE. In our study 22 of 250 patients (8.8%) had recurrent VTE and 8% were suspected recurrent VTE. In a randomized, open-label multicenter trial [7], Meyer et al. compared subcutaneous enoxaparin sodium (1.5 mg/kg once a day) with warfarin given for 3 months in 146 patients with VTE and cancer. The combined outcome event defined as major bleeding or recurrent VTE within 3 months. Of the 67 evaluable patients assigned to receive enoxaparin, 2.8% experienced recurrent VTE compared of the 7.2% in the present study. But excluded criteria were stricter. In our study, most of the recurrent VTE occurred under anticoagulation treatment according to the international guidelines. In a study conducted by Prandoni [4], the 12-month cumulative incidence of recurrent VTE in cancer patients during anticoagulant treatment (VKA) was 20.7%. Most of the events also occurred during the first month.

Like others published data, adenocarcinoma was the main histology. Lung, colorectal, prostate and breath cancer were the most frequent cancer. None tumor site increased the recurrent risk. Non Hodgkin lymphoma (NHL) seemed to be associated with an increase recurrent risk but this is statistically non significant reported to the exposed risk period. NHL had a longer life expectancy than neuroendocrine tumors or sarcoma. Patients with neuroendocrine tumors and sarcoma seemed to have an increase recurrent risk of VTE.

Most of the patients had a metastatic disease and underwent cancer treatment. In a systematic review [3], Louzada et al sought to evaluate cancer characteristics that may influence the risk for VTE recurrence. They included four retrospective and six prospective studies. VTE recurrence rate according to tumor stage suggested an increased risk for patients with metastatic malignancy compared with patients with localized disease (relative risk 1.36; 95% confidence interval 1.06-1.74. P = 0.01). In our study, metastatic disease was not associated

with an increase recurrent risk of VTE at six month but seemed to have an impact at long term. This result suggested that metastatic patient were treated according to the guidelines with prolonged treatment.

Interestingly, a major reversible risk factor during the initial VTE did not decrease the recurrent risk of VTE in our study population of patients with active cancer. The recurrent risk was increased after cancer surgical treatment: both tumor type and resection magnitude may impact VTE risk. In our study, 14.8% of the initial VTE occurred after cancer surgical treatment (abdominal and pelvic surgery in 74%). Cancer surgical treatment did not decrease the recurrent VTE, on the contrary, patients who underwent a cancer surgical treatment and who had a VTE after the surgery seemed to have an increased recurrent VTE risk during the first six month. These recurrent VTE occurred under treatment during the first three month after surgery or immediately when the treatment was stopped. This is a high-risk population. There was a positive interaction between “stopped anticoagulation” and “surgery” with an increased risk of VTE at six month (OR 12.45 CI 95% [1.66-99.65] p=0.014). These patients seemed to have a shorter duration of ACT (anticoagulation treatment). That could be explained because cancer surgery treatment was assimilated as a reversible major factor of VTE.

Some cancer treatments were known to increase the VTE risk in the cancer population. Chemotherapy for cancer, either as primary or adjuvant therapy, is associated with a 2-to 6-fold increased risk of VTE compared to the general population .Hormone therapy increase this risk, mainly breast cancer hormonotherapy. Among chemotherapeutic agents, cisplatin-based regimens particularly have been associated with a wide range of VTE [16-18].

Park et al. [17] analyzed VTE from Asian patients enrolled a prospective cohort study. All patients were newly diagnosed Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). All cases of VTE occurred in patients receiving chemotherapy whereas no VTE in patients without chemotherapy. In our study 48% of the VTE occurred under chemotherapy. The VTE rate seemed to increase with the new cancer treatments. Antiangiogenic agents seemed to be associated with increased VTE risk, but anti-tumor treatment regimens involving combination of chemotherapy plus antiangiogenic agents. In our study, chemotherapy did not impact the recurrent VTE. None of initial cancer treatment did it. We could not analyze the impact of cancer treatment during the recurrent VTE because of the lack of these data for non recurrent VTE patient. When anticoagulation was stopped after a major bleeding, the recurrent VTE was increased. It was difficult to treat VTE in cancer patient when major bleeding occurred, especially after cancer surgical treatment and to balance the risk-benefit.

The different international guidelines suggested that after 3 to 6 months, termination or continuation of anticoagulation (LMWH or VKA) should be based on individual evaluation of the benefit-risk ratio, tolerability, patients ‘preference and cancer activity. But the efficacy and safety of a prolonged treatment after six months is actually unknown.Our recurrent rate of VTE was 8 fold increased risk when anticoagulation (especially tinzaparin) was stopped during the first six months. These observations were according to the guidelines: 6 months of anticoagulation were necessary. After this period, the cessation of anticoagulation and the VKA relay did not impact the recurrent rate of VTE. A cessation of anticoagulation after a major bleeding just seemed to increase the recurrent VTE.

Palareti et al. [19] compared the outcome of anticoagulation courses in patients with malignancy with those without malignancy. The rates of major (5.4% vs 0.9%), minor (16.2% vs 3.6%) and total (21.6% vs 4.5%) bleeding were statistically significantly higher in cancer

patients compared with patients without cancer. In the group of patients with cancer, the bleeding rate was high during the first month, was high across the different INR categories and was independent of the temporally associated International Normalized Ratio (INR) [3, 19]. In our study, bleeding risk was increased during the third months under anticoagulation (VKA or tinzaparin) and the major bleeding rate was similar of the main clinical trials. The minor bleeding rate was lower than the main clinical trials. But this minor bleeding rate was under estimated in this retrospective study. In the clot study [5], the major bleeding rate was 6% and the global bleeding rate was 14%. In the study conducted by Meyer et al [7], the major bleeding rate was 7%, there was no lethal event. In our study, 3 bleeding were lethal event (16.7%). This rate was higher than the clinical trial but was more represented of the real life with less surveillance.

LMWHs seemed to have a lower major bleeding rate in cancer patient than in the general population. Kuderer conducted a comprehensive, systematic review and meta-analysis of the evidence from randomized controlled trials, to evaluate the impact of anticoagulants on survival and safety in cancer patients [20]. Major bleeding episodes occurred less frequently in patients who received LMWH (1%) compared with patients who received VKA (11.5%; $P < 0.0001$). In our study, major bleeding occurred in 83.3% in patients who received tinzaparin and 16.7% in patients who received VKA. The switch tinzaparin-VKA did not increase the bleeding risk. We observed that Radiotherapy (thoracic) and comorbidities increased the major bleeding events during anticoagulation in our study, like in others studies [21]. After the first six months, anticoagulation (tinzaparin or VKA) was well tolerated and did not increase the major bleeding rate.

The mortality rate was 42.8%. The three month mortality rate was 16.8% in patient who received tinzaparin. It was difficult to evaluate the impact of the anticoagulation

discontinuation on mortality. The mortality rate mainly depended on cancer prognosis. The mortality rate at 3 months in our study was 25.2% and is similar of the findings from the RIETE registry in Cancer (26.4%) [22].

The mortality rates in patients who received tinzaparin, anticoagulation and in the entire cohort at 12 month were not so different. The mortality rate at 24 months was more different: 28.4% in patient who received tinzaparin, 34.4% in patient who received anticoagulation and 39.6% in the cohort.

Major bleeding caused discontinuation of the anticoagulation increased the mortality rate. When clinician stopped the anticoagulation because of a considered good duration of anticoagulation, the mortality rate was increased. This was certainly due to good practice according to the international guidelines. We did not describe any decrease in the mortality rate with a prolonged duration of anticoagulation.

Our study suffers from limitations that are common to retrospective studies using database: the lack of information and the uncompleted follow-up. There was a problem of independence between data: tumor type, histology, duration of anticoagulation. The study's design tried to limit this.

Conclusion:

Patients with malign disease had a higher bleeding risk and a higher recurrent risk of VTE after a first event and with anticoagulation according to the international guidelines. These patient were well carried out, especially patients with a metastatic stage or an active cancer. Furthermore, patients considered with a lower recurrent risk factor because of a « provoked » first event (after a surgery) were not well carried out: they had a major recurrent risk of VTE.

The recurrent rate was mainly higher during the six first months. When the anticoagulation was stopped before the sixth month, the risk was eight fold higher. After six months, there

was no impact of the anticoagulation stop or the VKA switch on the recurrent rate or the mortality rate, when patient was treated according to the guidelines. Major bleeding seemed to increase the recurrence and increase the mortality rate when it caused the stop of the anticoagulation. The benefic-risk balance was difficult to equilibrate in this population.

Addendum

E. Noel-savina, O. Sanchez and F Couturaud: contribution to concept and design, analysis and interpretation of data; critical writing and revising the intellectual content; and final approval of the version to be published. R. Descourt: contribution to concept and design, critical writing and revising the intellectual content; and final approval of the version to be published. M. Andre, G. Meyer and C. Leroyer: critical writing and revising the intellectual content; and final approval of the version to be published.

Disclosure of conflict of interests

No conflict of interest.

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Table 1: Patients characteristics (N: 250)

Patients characteristics	N	(%)
Sex	M: 128 W: 122	51.2 48.8
VTE revealing cancer	26	10.7
VTE during the first 3 months after cancer diagnosis	55	22.6
Performance status :		
0	29	15.4
1	101	53.7
2	38	20.2
3	18	9.6
4	2	1.1
Metastasis	137	55
Recurrence	46	18.4
VTE on preventive anticoagulation	20	8.1
VTE on curative anticoagulation	10	3.9
Reversible major risk factor	71	28.5
- Prolonged immobilization	31	12.4
- Cancer surgery	40	16.1
Minor risk factor	15	6
VTE personal history	38	15.3
PE	64	25.8
DVT	71	28.6
PE + DVT	113	45.6
Switch VKA	66	26.6
Cancer Localization		
- Lung	69	27.6
- ENT	7	2.8
- Hematological Malignancy	25	10
Gynecological	49	19.6
- Prostate	26	10.4
- Digestive	47	18.8
- Kidney	11	4.4
- Others	15	6
Histology		
- Adenocarcinoma	163	65.2
- Epidermoid	22	8.8
- Neuroendocrin	13	5.2
- Non hodgkinian lymphoma	10	4
- Myeloma	9	3.6
- Others	35	14

Table 2: events at 6 months and after in terms of anticoagulation

	At 6 months	**After 6 months**	**Total** median length of follow-up 396 days
Recurrent VTE	**26** 22 on tinzaparin 2 on VKA 2 without AC	**20** 10 on tinzaparin 2 on VKA 8 without AC	**46**
Major bleeding	**14** 14 on tinzaparin 0 on VKA 0 without AC	**4** 1 on tinzaparin 3 on VKA 0 without AC	**18**
Death	**63** 54 on tinzaparin 5 on VKA 4 without AC	**44** 17 on tinzaparin 10 on VKA 17 without AC	**107**

Table 3: Characteristics of recurrent VTE patients (N= 46)

Recurrent VTE	**At six months N = 26**	**(%)**	**After six months N= 20**	**(%)**
Sex				
- M	15	33	10	22
- W	11	24	10	22
Metastasis	14	30	10	22
Active cancer	7	15	9	20
Treated cancer	17	37	9	20
Remission at the time of recurrence	0	0	3	6
No reversible major risk factor	16	35	19	41
Reversible major risk factor	10	22	6	13
- prolonged immobilization	3	6	3	6
- surgery	7	15	3	6
Minor risk factor	0	0	2	4
VTE				
- PE	10	22	9	20
- PE + DVT	2	4	5	11
- DVT	9	20	6	13
- Venous central catheter	2	4	0	0
Recurrence on anticoagulant	21	45	8	17
- Tinzaparin	21	45	5	11
- VKA	0	0	3	6
No anticoagulation	5	11	12	26
Same presentation as the first VTE	9	20	5	11
Suspected	24	52	18	40
Unsuspected and no symptom	2	4	1	2
Unsuspected and symptoms	0	0	1	2
Fatal recurrent	7	15	1	2

Highlights

Six months of treatment for VTE in patients with cancer are needed.

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Be careful of a « provoked » first event (after surgery).

The recurrent rate was mainly higher during the six first months.

When anticoagulation was stopped before sixth month, the risk was eight fold higher.

After six months: no impact of the type of anticoagulation on the recurrent rate.