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SHORT COMMUNICATIONS

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UPPER EXTREMITY DVT IN ONCOLOGICAL PATIENTS: ANALYSIS OF RISK FACTORS. DATA FROM THE RIETE REGISTRY

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Aim: **The aim of the study is to up date informations on the clinical characteristics and outcome of patients with upper-extremity deep vein thrombosis (DVT) from the Informatised Registry on Venous Thromboembolism (RIETE).** ***Methods:*** **RIETE is an ongoing registry of consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism. In this analysis the clinical characteristics and 3-month outcome of all cancer patients with upper-extremity DVT were evaluated.** ***Results:*** **Up to February 2006, a total of 14,391 patients with symptomatic, objectively confirmed acute venous thromboembolism had been enrolled in RIETE. Of the 2,945 patients with active cancer 196 (6.7%) had arm DVT: 104 had catheter-associated DVT. Most cancer patients with arm DVT were males, younger than 65, and had a low incidence of additional risk factors or underlying diseases. Twenty of them (10%) had symptomatic pulmonary embolism (PE). Most patients were treated with low-molecular-weigh heparin, both initially (94%) and after discharge (75%). During the 3-month follow-up period 12 patients (6.1%) developed VTE recurrences (PE 6, DVT 6), 8 (4.1%) had major bleeding (fatal in 3), 43 (22%) died.** ***Conclusions:*** **Our data from the RIETE registry show that upper limb DVT is a serious complication in patients with cancer, with a high incidence of recurrences and bleeding complications.**
Key Words**: cancer, catheter, vein, thrombosis, risk factor.**

Patients with cancer are more prone to develop venous thromboembolism (VTE), due to the hypercoagulable state caused by the malignancy, but also to other additive risk factors, such as mechanical injury of the venous endothelium by the use of intravenous catheters and irritation of vessel walls by chemotherapy. In cancer patients who develop VTE the risk of death is more than threefold than in patients without cancer who have VTE [1–3] and in those with cancer but no VTE [4]. This high mortality rate is probably due to both the VTE and the fact that malignancies associated with VTE appear to follow a more aggressive course [4]. Thus, identifying clinical characteristics that put cancer patients at increased risk of VTE is important if their outcomes are to be improved.

Upper-extremity deep vein thrombosis (DVT) was long believed to be an uncommon disorder caused by malrotation of the upper extremity, especially when associated with strenuous exercise. However, with the increasingly common use of intravenous catheters, arm DVT has been recognised as being more common than previously reported, but its frequency continues to be much lower than that of lower limb DVT. Accordingly, there is little information on the clinical characteristics and outcome of these patients.

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Abbreviations used: AVK – anti-vitamin K; CI – confidence intervals; DVT – deep vein thrombosis; LMWH – low-molecular-weight heparin; PE – pulmonary embolism; RIETE – Informatised Registry on Venous Thromboembolism; UFH – unfractionated heparin; VTE – venous thromboembolism.

The Informatised Registry on Venous Thromboembolism (RIETE) was initiated in March 2001 to prospectively record the current clinical management of VTE. It is an ongoing, multicenter, observational registry designed to gather and analyze data on treatment patterns and clinical outcomes in consecutive patients with symptomatic, objectively confirmed, acute VTE [5–9]. The aim of the present study was to identify the clinical characteristics and 3-month outcome of all cancer patients with upper-extremity deep venous thrombosis (DVT) enrolled in RIETE.

PATIENTS AND METHODS

Consecutive patients with symptomatic, acute DVT or pulmonary embolism (PE), confirmed by objective tests are enrolled in RIETE.

Variables. The parameters recorded by the registry comprise details of each patient's baseline characteristics; clinical status, including any coexisting or underlying conditions; cancer characteristics; the type, dose, and duration of treatment received on VTE diagnosis, and clinical outcome during the first 3 months of therapy.

Clinical definitions. Immobilized patients are defined in this analysis as non-surgical patients who had been immobilized (i. e., total bed rest with bathroom privileges) for $\geqslant$ 4 days in the 2-month period prior to VTE diagnosis. Surgical patients are defined as those who had undergone an operation in the 2 months prior to VTE diagnosis. Fatal PE was defined as any death occurring shortly (< 7 days) after PE diagnosis (either the initial episode or recurrent PE), in the absence of an alternative cause of death. Fatal bleeding was defined

as any death occurring shortly (< 7 days) after a major bleeding episode. Bleeding complications were classified as "major" if they were overt and were associated with a decrease in hemoglobin level of ⩾ 2.0 g/dL, required a transfusion of ⩾ 2 units of blood, or were retroperitoneal or intracranial.

Follow-up. After hospital discharge, all patients were followed-up for at least 3 months. During each visit, any signs or symptoms suggesting either DVT or PE recurrence or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was documented by repeat compression ultrasonography, venography, lung scanning, helical CT scan or pulmonary angiography.

Statistical analysis. Odds ratios and corresponding 95% confidence intervals were calculated using Confidence Interval Analysis software (version 2.0.0), and $p < 0.05$ was considered to be statistically significant. The significance of a number of clinical variables on the mortality rate was tested by Chi-Square test for categorical variables and by t-test for numerical variables. Candidate variables were selected from clinical variables based on published literature and on expert opinion.

RESULTS

Up to Febrary 2006, a total of 14,391 patients with symptomatic, objectively confirmed acute VTE had been enrolled in RIETE and followed-up for up to 3 months. Of the 2,945 patients with active cancer 196 (6.7%) had arm DVT. One hundred and four of them (53%) had catheter-associated DVT (central line 37, port system 37, peripheral line 8, stent 6, pacemaker one).

Most cancer patients with arm DVT were males, younger than 65, and had a low incidence of additional risk factors or underlying diseases. Twenty of these patients (10%) had both clinical signs and objective diagnosis of PE. Most patients were treated with low-molecular-weigh heparin, both initially (94%) and after discharge (75%). During the 3-month follow-up period 12 patients (6.1%) developed VTE recurrences (PE 6, DVT 6), 8 (4.1%) had major bleeding (fatal in 3).

Patients with catheter-associated DVT had more often a recent episode of surgery, and less often chronic lung disease than those with no catheter, as shown in the Table. Right-side DVT was more common in these patients. They had less often metastatic cancer, and appeared more commonly in patients with colorectal cancer, but less often in lung cancer. During follow-up, the rates of fatal PE, recurrent VTE, fatal bleeding and major bleeding were similar, but overall death was higher in patients with no catheter.

DISCUSSION

The data in this analysis, obtained from a large prospective series of consecutively enrolled patients in the RIETE registry, confirm that arm DVT is an uncommon complication in patients with cancer compared to lower-extremity DVT. There was a similar incidence in patients with or without catheter, and one in every 10 patients had concomitant PE. As for their clinical outcome, the 6.1% incidence of recurrences and the 4.1% of major bleeding is similar to the reported rates in patients with lower limb DVT while on anticoagulation [10].

Table. Clinical characteristics and 3-month outcome of the 196 patients with cancer and upper-extremity DVT

Variables	Catheter N = 104	No catheter N = 92	Odds ratio (95% CI)	P value
Clinical characteristics,				
Gender (males)	59 (57%)	63 (69%)	0.6 (0.3–1.1)	0.090
Age > 65 years	39 (38%)	39 (42%)	0.8 (0.5–1.4)	0.485
Body weight < 70 kg	54 (52%)	46 (50%)	1.1 (0.6–1.9)	0.788
Underlying diseases,				
Creatinine levels > 1.2 mg/dL	11 (11%)	5 (5.4%)	2.1 (0.7–6.2)	0.189
Chronic lung disease	4 (3.8%)	12 (13%)	0.3 (0.1–0.9)	0.019
Chronic heart failure	2 (1.9%)	6 (6.5%)	0.3 (0.1–1.4)	0.104
Risk factors for VTE,				
Immobility ⩾ 4 days	5 (4.8%)	8 (8.7%)	0.5 (0.2–1.7)	0.275
Surgery < 2 months	29 (28%)	12 (13%)	2.6 (1.2–5.4)	0.011
Prior VTE	5 (4.8%)	8 (8.7%)	0.5 (0.2–1.7)	0.275
Cancer characteristics,				
Metastatic cancer	51 (49%)	58 (63%)	0.6 (0.3–1.0)	0.049
Site of cancer:				
Lung	23 (22%)	32 (35%)	0.5 (0.3–1.0)	0.050
Breast	13 (13%)	14 (15%)	0.8 (0.4–1.8)	0.582
Colorectal	23 (22%)	5 (5.4%)	4.9 (1.8–14)	0.001
Stomach	11 (11%)	4 (4.3%)	2.6 (0.8–8.5)	0.102
Haematological	10 (9.6%)	5 (5.4%)	1.6 (0.6–5.6)	0.272
Other	24 (23%)	32 (35%)	0.6 (0.3–1.1)	0.070
Clinical presentation,				
Symptomatic PE	10 (9.6%)	10 (11%)	0.9 (0.3–2.4)	0.773
Left side DVT	35 (34%)	45 (50%)	0.5 (0.3–1.0)	0.030
Bilateral DVT	5 (4.8%)	10 (11%)	0.4 (0.1–1.4)	0.112
Initial therapy,				
UFH	3 (2.9%)	5 (5.4%)	0.5 (0.1–2.6)	0.369
LMWH	98 (94%)	87 (95%)	0.9 (0.2–3.6)	0.919
Long-term therapy,				
AVK drugs	23 (22%)	22 (24%)	0.9 (0.4–1.8)	0.765
LMWH	75 (72%)	63 (68%)	1.2 (0.6–2.3)	0.578
3-month outcome,				
Major bleeding	4 (3.8%)	4 (4.3%)	0.9 (0.2–3.6)	0.859
Fatal bleeding	1 (1.0%)	2 (2.2%)	0.4 (0.1–4.9)	0.490
Recurrent DVT	4 (3.8%)	2 (2.2%)	1.8 (0.3–10)	0.498
Recurrent PE	4 (3.8%)	2 (2.2%)	1.8 (0.3–10)	0.498
Fatal PE	1 (1.0%)	0	–	0.346
Overall mortality	17 (16%)	26 (28%)	0.5 (0.2–1.0)	0.044

Traditionally, the significance of arm DVT has received less attention in comparison to lower extremities DVT, probably due to the erroneous belief that accompanying or subsequent PE is rare. Accordingly, in the past several authors have questioned the need for anticoagulant therapy in such patients. However, recent prospective studies using sensitive methods for detecting PE have demonstrated that the prevalence of both symptomatic and asymptomatic PE in patients with arm DVT is high, and it is close to that observed in cohorts of patients with lower-extremity DVT [11–14]. One in every ten patients with arm DVT in our series had symptomatic PE, thus confirming these findings.

The main limitation of this study lies on the likely underestimated incidence rate of fatal PE after discharge. Certainly, death of some cancer patients at home or in long-term care facilities may have been due to PE, but these but may not have been labeled as induced by PE as the Adjudication Committee only accepts VTE events that have been objectively confirmed. On the other hand, in the RIETE registry selection bias was avoided by including consecutive patients with objectively confirmed, symptomatic, acute VTE who were referred to study cen-

ters. Enrolled patients were treated according to standard practice, and prospective follow-up was completed for all patients. Objective criteria were strictly applied for the diagnosis of initial and recurrent VTE, including contrast venography and pulmonary angiography if indicated, and major bleeding was classified according to widely accepted and validated criteria.

We conclude that arm DVT is a serious complication in patients with cancer, with a high recurrence rate despite anticoagulant therapy, as well as a high incidence of severe bleeding complications. Accordingly, adequate identification of patients at risk, effective and safe prophylaxis, and early confirmation of diagnosis is warranted.

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ПРОБЛЕМА ТРОМБОЗА ГЛУБОКИХ ВЕН У БОЛЬНЫХ ОНКОЛОГИЧЕСКОГО ПРОФИЛЯ: АНАЛИЗ ФАКТОРОВ РИСКА. ДАННЫЕ РЕГИСТРА RIETE

Цель: **обновить базу данных по клиническим характеристикам и течению заболевания у больных с тромбозом глубоких вен верхних конечностей (ТГВ) с использованием системы регистра венозного тромбоэмболизма (СРВТ).** ***Методы:*** **СРВТ является непрерывной системой регистрации больных с симптомами объективно подтвержденной острой венозной тромбоэмболии. Проанализированы клинические характеристики и течение болезни на протяжении месяцев у больных онкологического профиля с ТГВ.** ***Результаты:*** **в период декабря 2006 г. были обследованы 14 391 больных с симптоматической объективно подтвержденной острой венозной тромбоэмболией при помощи системы СРВТ. Из 2945 больных с прогрессирующим течением заболевания у196 (6,7%) человек выявили ТГВ верхних конечностей: у 104 — ассоциированный с катетером ТГВ. Большинство больных с ТГВ верхних конечностей — лица мужского пола в возрасте моложе 65 лет и с низкой частотой дополнительных факторов риска или первичного заболевания. У 20 из них (10%) отмечали симптомы эмболии легочной артерии (ЭЛА). Больные получали низкомолекулярный гепарин и в начале исследования (94%), и по его окончании (75%). В течение последующих трех месяцев у12 больных (6,1%) развился рецидив венозной тромбоэмболии (ВТЭ) (ЭЛА – у 6 больных, ТГВ – у 6 больных), у 8 (4,1%) отмечали кровотечение (3 случая с летальным исходом), 43 (22%) пациента умерли.** ***Выводы:*** **данные СРВТ системы показали, что ТГВ верхних конечностей является серьезным осложнением у больных, онкологического профиля, сочетающимся с высокой степенью развития рецидива и осложнений, сопровождающихся кровотечениями.**

***Ключевые слова*: рак, катетер, вена, тромбоз, фактор риска.**