original article

Annals of Oncology 22: 2101–2106, 2011
doi:10.1093/annonc/mdq720
Published online 16 February 2011

Incidental versus symptomatic venous thrombosis in cancer: a prospective observational study of 340 consecutive patients

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Received 26 May 2010; revised 25 August 2010; accepted 15 November 2010

Background: The clinical significance of incidental venous thrombosis (IVT) is uncertain. The objective of this study was to compare the clinical characteristics and the outcome of cancer patients with IVT with those of patients with symptomatic venous thrombosis (SVT).

Patients and methods: Prospective observational study enrolling consecutive cancer patients newly diagnosed with venous thromboembolism (May 2006–April 2009). Diagnosis of IVT was based on vascular filling defects in scheduled computed tomography scans in the absence of clinical symptoms. Anticoagulant therapy was routinely prescribed regardless of SVT or IVT.

Results: IVT was diagnosed in 94 out of 340 (28%) patients. Patients with IVT were older (63.7 ± 10.5 versus 60.8 ± 10.5 years, $P = 0.035$), more frequently had metastatic cancer (82% versus 65%, $P = 0.01$) and were less likely to be receiving chemotherapy at the time of the thrombotic event (53% versus 67%, $P = 0.018$). Mean follow-up was 477 days. A lower risk of venous rethromboses was observed in patients with IVT (log-rank $P = 0.043$), with no differences in major bleeding and overall survival compared with SVT patients.

Conclusions: A high proportion of venous thrombotic events in cancer patients are diagnosed incidentally during scheduled imaging. Prospective controlled trials evaluating the optimal therapy in this setting are required.

Key words: cancer-related venous thromboembolism, incidental thrombosis, symptomatic thrombosis

introduction

Venous thrombosis (VT) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is the main manifestation of the hypercoagulable state associated with cancer and a leading cause of death and morbidity in this population [1, 2]. Anticoagulant therapy for VT is more challenging in cancer patients due to a higher incidence of both recurrent thrombotic events and bleeding complications compared with cancer-free patients with VT [3]. Moreover, the gradual increase in life expectancy in cancer patients achieved in recent years implies that patients with a larger number of comorbidities receive active anticancer therapy for longer periods of time. Therefore, there is growing concern among oncologists with respect to primary thromboprophylaxis and anticoagulant therapy once VT is established [4–6].

The widespread use and progressive development of imaging techniques in recent years have led to an increase in diagnoses of unsuspected or incidental venous thrombosis (IVT), especially silent PE, with most of the available information on the prevalence of IVT being provided by imaging studies [7–9], while most clinical studies of VT in cancer patients have focused on symptomatic venous thrombosis (SVT) [10–13].

The latest American College of Chest Physicians guidelines for the treatment of VT [14] specifically recommend the use of the same initial and long-term anticoagulant treatment for IVT and for comparable patients with SVT, although no randomized studies support this approach (grade 1C evidence) [15]. Similar recommendations have recently been issued for the treatment of IVT in patients with cancer [5], although there are little data on the potential benefits and safety of anticoagulant therapy in these cancer patients.

The objective of this study was to prospectively assess the epidemiology, clinical characteristics and outcomes of cancer patients with newly diagnosed VT according to the presence or absence of VT symptoms at diagnosis.

patients and methods

patients

A prospective observational study consecutively enrolling adult patients with cancer and newly diagnosed VT was carried out in our Medical

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Oncology Department from May 2006 to April 2009 in the Hospital Clinic of Barcelona, a tertiary teaching hospital with a reference population of >500 000 inhabitants. All patients included in the study had histologically confirmed solid tumors and were eligible if they had either active cancer (locoregional or metastatic) or developed VT while receiving adjuvant chemotherapy.

The new VT event at study recruitment was named VT index event. Patients were recruited in the cancer outpatient clinics (clinically stable patients attended during the daytime from Monday to Friday), in the Emergency Department (clinically unstable patients and/or during nights and weekends) and in the Medical Oncology ward for hospitalized patients. All VT index events were diagnosed as part of routine clinical practice and were assessed directly by the authors at VT diagnosis whenever possible or after a maximum of 72 h.

VT events incidentally found in scheduled computed tomography (CT) (SCT) scans carried out for cancer evaluation as part of usual staging practice (mostly during the daytime from Monday to Friday) were reported to the on-call oncologist who clinically evaluated the patient. Clinical assessment included a medical interview and physical examination including vital signs (blood pressure, heart and respiratory rates) and pulsioxymetry. IVT was defined as a thrombus accidentally found in a SCT scan carried out for malignant disease evaluation in patients with no symptoms indicative of VT (new chest pain, syncope, significant difficulty in breathing and/or limb edema). Patients with coexisting SVT and IVT events in different corporal regions were also classified as having SVT.

The clinical assessment was recorded on a standardized data collection sheet that included information on clinical symptoms, demographics, vascular risk factors, performance status using the Eastern Cooperative Oncology Group classification, tumor type and stage [16], specific anticancer therapy received in the 2 months before the diagnosis of VT (surgery, chemoradiotherapy and hormonotherapy), catheter insertion and use of erythropoiesis-stimulating agents at the time of the VT index event. The study was approved by the Hospital Ethics Committee. All patients provided written informed consent to participate in the study.

imaging studies

All VT events were confirmed using objective radiological methods. Patients underwent SCT scans for oncological assessment according to routine clinical practice. SCT scans were carried out using a dual CT scanner (Somatom scanner; Siemens Medical Solutions, Somatom Healthcare, Erlangen, Germany) with an intravenous injection of 100 ml of non-ionic contrast medium (300 mg/ml) injected at a rate of 3 ml/s. SCT of the thorax was carried out with an automatic detection (care bolus) of contrast in the ascending aorta, 1.2 mm collimation and 5 mm reconstruction. SCT of the abdomen and pelvis from the diaphragm to the pubic symphysis was carried out 70–90 s after the injection of contrast medium for chest CT.

When the SCT scan was inconclusive for PE or the patient complained of symptoms indicative of PE, a new multislice CT scan specific for the depiction of PE was carried out with the 64 multidetector CT scan, with 0.6 mm collimation and 1 mm reconstruction including angiography of the pulmonary arteries and lower limb venography (CTPA). A thrombus in either SCT or CTPA was defined as a definite intraluminal filling defect seen on at least two consecutive transverse images and contrasted by two senior radiologists.

Patients with clinical symptoms of PE who had contraindications for a CTPA scan (renal failure and/or allergy to iodine contrast) underwent ventilation/perfusion pulmonary scintigraphy (VPPS) using Tc-99. Only images with a high probability according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study criteria were considered diagnostic of PE [17].

PE was classified according to three dichotomic variables: central (main and lobar arteries) or peripheral (segmental or subsegmental branches), single or multiple, and unilateral or bilateral according to whether PE involved either one or both lungs.

In patients with suspected DVT in the upper or lower limbs, a B-mode and color-Doppler ultrasound examination (Duplex US) was carried out. DVT was diagnosed when the lumen of the vessel was not compressible or when a flow defect was present in the Doppler study.

therapy

Anticoagulant therapy was prescribed by the treating oncologists according to current international recommendations at the time of the study [14,18] including clinical evidence available from the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators study [19]. The therapeutic approach to VT was the same regardless of whether the patient had SVT or IVT. Low-molecular-weight heparin (LMWH) was the standard anticoagulant therapy during the first 3 months after the VT index event. Subsequently, LMWH was also routinely recommended for 6–12 months or even indefinitely for patients with active neoplastic disease and/or those receiving chemotherapy. Switching to oral anticoagulation (OAC) from LMWH was allowed in patients reluctant to receive daily injections. The decision to avoid or discontinue anticoagulant therapy because of bleeding events was made individually by treating physicians according to the clinical status.

follow-up

Follow-up was ongoing up to the death of the patient (including death in the first 24 h after the diagnosis of VT) or the last follow-up at the time of data analysis (May 2010). The database was updated monthly by the authors according to the clinical information available on scheduled oncologist visits, hospital admissions, electronic health records and/or telephone calls if necessary. The data recorded included maintenance of anticoagulation, venous rethrombosis, relevant bleeding and date and cause of death.

The duration of anticoagulant treatment was classified into three categories based on clinical practice: (i) indefinite LMWH or alternating LMWH/OAC therapy (when anticoagulation was maintained from the VT index event up to death or the last follow-up), (ii) LMWH for 6 months (most common strategy when VT occurred in the adjuvant chemotherapy setting) and (iii) therapy with LMWH for ≤3 months (in patients in whom anticoagulant treatment was intentionally discontinued due to adverse events or physician decision based on individual risk–benefit assessment).

Venous rethrombosis during the follow-up was defined as new VT occurring at another site and/or extension of the thrombus found in the previous baseline evaluation.

A bleeding event was classified as major when it was associated with death, occurred at a critical site (intracranial, intraspinal, intraocular, retroperitoneal or pericardial region), required blood transfusions or resulted in a fall in hemoglobin of at least 2 g/dl [19].

Causes of death were classified into five categories: cancer progression, bleeding, intercurrent infection, arterial thrombosis and venous thromboembolism.

statistical analysis

Baseline characteristics of the patients were reported by means and standard deviation, and absolute numbers and percentage. Categorical variables were compared by the chi-square or Fisher's exact tests as appropriate. Continuous variables were compared using the Student's *t*-test. Mean follow-up times were calculated from the VT index event until the death of the patient or the last follow-up. Cumulative major bleeding events, venous rethrombosis-free survival and overall survival were estimated using the Kaplan–Meier method, and comparisons between the two patient groups were made using

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the log-rank test. Overall survival, venous rethrombosis-free survival and major bleeding-free survival were calculated as the time from the VT index event to death, venous rethrombosis or major bleeding events, respectively, or censored data (death or last follow-up).

Multivariate analyzes were carried out with a stepwise Cox proportional hazard ratio model using independent variables identified in the univariate analysis. Exp(beta) and their corresponding 95% confidence intervals (95% CI) were calculated. Statistical significance was established as $P < 0.05$ (two-tailed). Calculations were carried out using the SPSS v14 package (SPSS Inc., Chicago IL).

results

patient characteristics

A total of 340 patients (193 males and 147 females) were included in the study. The VT index event was diagnosed with confirmatory examinations (162 Duplex US, 51 CTPA, 12 VPPS and 2 phlebographies) in 227 (67%) patients with symptoms of VT and by SCT scans in 113 (33%) patients, of whom 19 (17%) presented symptoms of VT at the clinical evaluation and were classified as having SVT. Therefore, the study groups consisted of 246 (72%) patients with SVT and 94 (28%) patients with IVT. Baseline epidemiological data are shown in Table 1. In the univariate analysis, patients with IVT were significantly older (mean age 63.7 ± 10.5 versus 60.8 ± 11.7 years; $P = 0.035$), were more likely to have metastatic disease (82% versus 65%; $P = 0.01$) and were less likely to be receiving chemotherapy at the detection of the thrombotic event by imaging (53% versus 67%; $P = 0.018$) than patients with SVT.

thrombotic events

IVT and SVT differed significantly ($P < 0.001$) according to the vascular territory involved (Table 2). In patients with IVT, the most frequent clinical presentation was PE (60%), thrombosis of the inferior vena cava (17%) and the iliac veins (10%). In contrast, patients with SVT mainly presented with thrombosis of the femoropopliteal territory (47%) followed by PE (26%), thrombosis of the subclavian and/or jugular veins (18%), proximal upper limb (4%) and the superior vena cava (3%).

The radiological findings in patients with PE are summarized in Table 3. A similar proportion of patients with SVT and IVT had PE involving the central arteries and coexisting with signs of lung infarction and DVT. The proportion of small peripheral PE was low (10% in SVT and 13% in IVT, not significant) in both groups. However, bilateral lung involvement was more frequent in symptomatic PE (65% versus 41%, $P < 0.009$) than incidental PE. Likewise, multiple PE tended to be more frequent in patients with SVT (87% versus 75%, $P = 0.08$) than in those with IVT, although the difference was not significant.

clinical outcome

Three patients were transferred to another institution during follow-up, but relevant clinical information was obtained from the patients and treating physicians by telephone calls. Table 4 shows the outcome variables, with a mean follow-up of 477 ± 435 days (range 1–1460 days). A higher proportion of patients with IVT had received <3 months of LMWH compared with patients with SVT (16% versus 4%, $P < 0.001$). There were no statistical differences with respect to major bleeding events and venous rethrombosis in patients with IVT or SVT. Likewise, no differences were observed in the proportion of patients who had died, mean survival after the VT index event and causes of death between IVT and SVT; neither were there differences in major bleeding events and overall survival in the Kaplan–Meier curves for the two groups (Figure 1A and B).

However, patients with SVT had a higher risk of venous rethrombosis compared with patients with IVT (Figure 1C). The rethrombosis-free survival rate at 180 and 365 days was 86.5% and 82% for SVT and 96% and 93% for IVT, respectively (log-rank $P = 0.043$). In the multivariate analysis of venous rethrombosis, the best model included the following variables: SVT (no = 0, yes = 1) [$P = 0.009$; exp(beta) = 2.366,

Table 1. Baseline characteristics of the study cohort at the time of the VT index event according to the presence of VT symptoms

	SVT (%) $N = 246$ (72)	IVT (%) $N = 94$ (28)	P
Mean age ± SD (years)	60.8 ± 11.7	63.7 ± 10.5	0.035
Male	135 (55)	58 (62)	NS
Smoking	131 (53)	46 (49)	NS
Diabetes	24 (10)	13 (14)	NS
Hypertension	70 (28)	27 (29)	NS
Dyslipidemia	37 (15)	14 (15)	NS
Previous VT before cancer	14 (6)	4 (4)	NS
Inpatients	37 (15)	10 (11)	NS
Performance status			NS
ECOG 0	42 (17)	10 (11)	
ECOG 1	91 (37)	41 (44)	
ECOG 2	71 (29)	33 (35)	
ECOG 3	42 (17)	10 (11)	
Tumor type			NS
Lung	59 (24)	26 (28)	
Colorectal	41 (17)	11 (12)	
Breast	39 (16)	10 (11)	
Genitourinary	29 (12)	14 (15)	
Gynecological	23 (9)	11 (12)	
Upper gastrointestinal[a]	21 (8)	11 (12)	
Head and neck	17 (7)	3 (3)	
Other[b]	17 (7)	8 (8)	
Tumor stage			0.01
Clinical remission	38 (15)	6 (6)	
Locoregional	47 (19)	11 (12)	
Metastatic	161 (65)	77 (82)	
Therapies			
Chemotherapy	165 (67)	50 (53)	0.018
Radiotherapy	62 (25)	27 (28)	NS
Hormonotherapy	20 (8)	11 (12)	NS
Major surgery	33 (13)	13 (14)	NS
ESA	58 (24)	24 (25)	NS

[a]Gastroesophagic ($n = 18$), pancreas ($n = 6$), biliary system ($n = 5$), neuroendocrine ($n = 3$).

[b]Melanoma ($n = 8$), cancer of unknown origin ($n = 8$), sarcoma ($n = 4$), central nervous system ($n = 2$), thymoma ($n = 2$), mesothelioma ($n = 1$).

VT, venous thrombosis; SVT, symptomatic venous thrombosis; IVT, incidental venous thrombosis; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group classification; ESA, erythropoiesis-stimulating agents; NS, not significant.

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Table 2. Site of the index VT in patients with SVT or IVT

	SVT (%) N = 246	IVT (%) N = 94
Femoropopliteal	116 (47)	6 (6)
Pulmonary embolism	63 (26)	56 (60)
Subclavian and/or jugular	45 (18)	5 (5)
Inferior vena cava	2 (1)	16 (17)
Proximal arm	10 (4)	1 (1)
Iliac veins	0	9 (10)
Superior vena cava	7 (3)	1 (1)
Cerebral veins	3 (1)	0
Indwelling catheter	43 (18)	1 (1)

VT, venous thrombosis; SVT, symptomatic venous thrombosis; IVT, incidental venous thrombosis.

Table 3. Radiological findings in patients with PE according to SVT and IVT

	SVT (%) N = 63	IVT (%) N = 56	*P*
Central arteries	33 (52)	36 (64)	NS
Bilateral	41 (65)	23 (41)	0.009
Multiple PE	55 (87)	42 (75)	NS
Single peripheral PE	6 (10)	7 (13)	NS
CT signs of lung infarction	3 (5)	2 (4)	NS
Associated DVT in CT scans	8 (13)	4 (7)	NS

PE, pulmonary embolism; SVT, symptomatic venous thrombosis; IVT, incidental venous thrombosis; CT, computed tomography; DVT, deep venous thrombosis.

Table 4. Outcomes of patients with SVT and IVT

	SVT (%) N = 246	IVT (%) N = 94	*P*
Anticoagulant therapy			0.003
Indefinite LMWH	127 (52)	48 (51)	
Indefinite LMWH/OAC	55 (22)	18 (19)	
6 months LMWH	53 (21)	13 (14)	
≤3 months LMWH	11 (4)	15 (16)	
Major bleeding	24 (10)	7 (7)	NS
Venous rethrombosis	44 (18)	10 (11)	NS
Deaths	175 (71)	67 (71)	NS
Cancer progression	133	58	
Infection	12	2	
Venous thromboembolism	13	3	
Arterial thrombosis	3	0	
Bleeding	14	4	
Mean survival after VT index event	469 ± 445	497 ± 405	NS

SVT, symptomatic venous thrombosis; IVT, incidental venous thrombosis; LMWH, low-molecular-weight heparin; OAC, oral anticoagulation; VT, venous thrombosis.

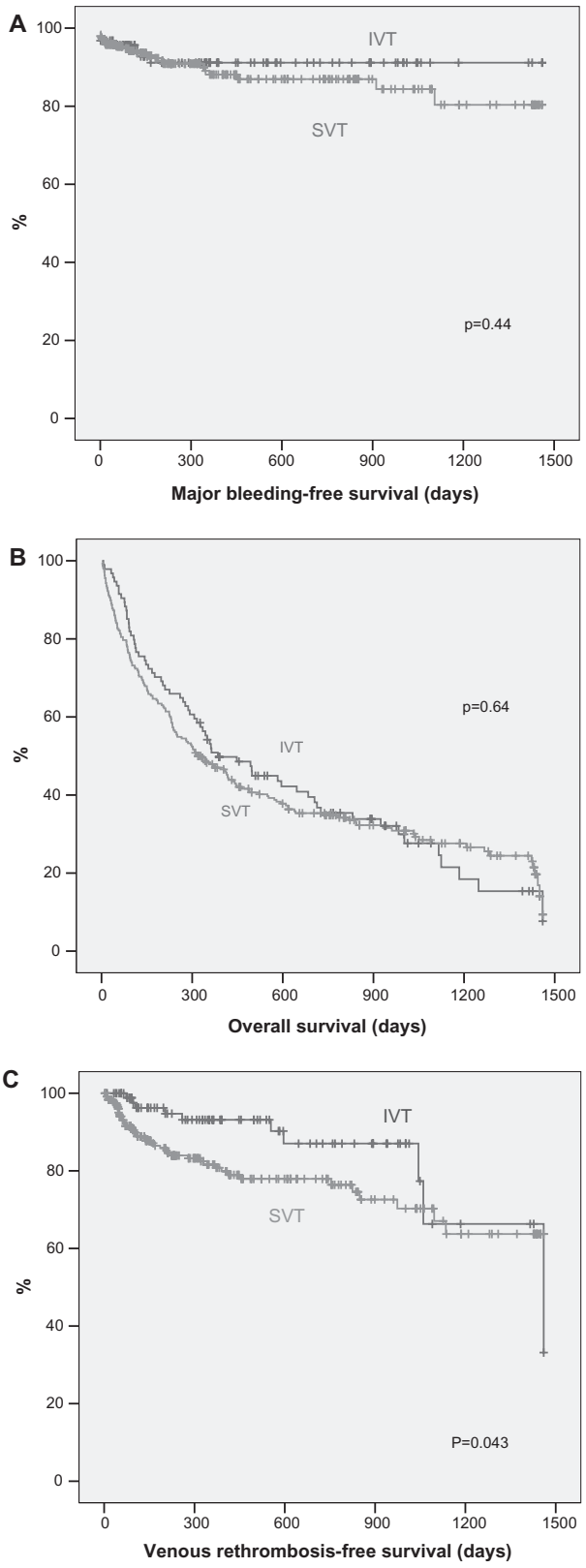

Figure 1. Kaplan–Meier curves of major bleeding-free survival (A), overall survival (B) and rethrombosis-free survival (C) in cancer patients according to symptomatic venous thrombosis (SVT) or incidental venous thrombosis (IVT).

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95% CI 1.176 to 4.759], cancer extension at the time of the VT index event (adjuvant chemotherapy = 0, locoregional cancer = 1, metastatic disease = 2) [$P = 0.009$; exp(beta) = 1.275, 95% CI 1.050 to 1.549].

discussion

To our knowledge, this is the first study to prospectively describe and compare the epidemiological characteristics, disease pattern and clinical outcome of a large cohort of cancer patients newly diagnosed with SVT or IVT.

VT is known to display a wide spectrum of clinical presentations including asymptomatic patients [14, 20], although most of the data on IVT in patients with cancer come from imaging studies, which may have underestimated its prevalence in clinical practice. Our results suggest that IVT is common, rather than sporadic, in this group of patients, as 28% of VT events and nearly half the PE were incidentally diagnosed and asymptomatic at clinical evaluation. Although different patterns of oncological practice may influence the detection of IVT according to the frequency of restaging CT scans, our results may taken as representative of the current standard of oncological practice in a tertiary cancer center. We found that IVT was more frequent in older patients with metastatic disease, possibly due to the larger number of imaging scans carried out during the follow-up, although another reasonable explanation could be that differences in the general clinical status of metastatic cancer patients (usually with more disease-related symptoms) could mask or delay the diagnosis of VT. A retrospective study of 59 cancer patients with unsuspected PE [21] found that up to 75% of patients were symptomatic, although neither the intensity nor the characteristics of the symptoms allowed the diagnosis of VT before the scheduled imaging test. In our series, 19 patients (17% of those diagnosed with SCT) initially classified as IVT were reclassified as SVT after clinical evaluation. It is also plausible that the finding of IVT may indicate a greater underlying prothrombotic activity (as a harbinger of symptomatic events) in patients with advanced cancer.

We also found that most thrombi in the IVT group involved large vessels (central PE, cava and iliac veins) as reported in radiological series of cancer patients, whereas most SVT occurred in the limbs. This is not surprising since SCTs are almost always restricted to the chest, abdomen or pelvis and the objective of our study was not to determine the incidence of asymptomatic distal DVT. Interestingly, comparison of the radiological findings in the chest showed few differences in the burden and distribution of PEs, which were small and peripheral in only a few cases, with a similar proportion in IVT and SVT patients. Although the clinical significance of small peripheral PE remains unclear [22, 23], the substantial burden of IVT observed in this study further supports current recommendations on the treatment of patients with IVT [5, 14].

Despite the lack of evidence on the treatment or not of patients with IVT, we considered that the pros (preventing rethrombosis, possible benefit in survival) of anticoagulation would probably outweigh the cons (risk of bleeding, patient discomfort) for treating these patients. However, our results show that patients with SVT received anticoagulants for longer periods than patients with IVT.

Even taking into account the inherent limitations of an observational study and the fact that a higher proportion of patients with IVT had received anticoagulant therapy for <3 months, better outcomes were observed in venous rethrombosis in patients with IVT, suggesting that patients with SVT might have more pronounced thrombotic diathesis than patients with IVT. However, other potential confounding factors (such as other medical comorbidities at baseline, subsequent medical events and anticancer therapies during follow-up), apart from the symptomatic or asymptomatic presentation of the thrombotic event could have influenced the differences observed in the occurrence of venous rethrombosis.

In summary, this study provides novel information on the epidemiology and impact of IVT in current clinical practice in cancer patients diagnosed with VT and shows that IVT is common, especially in patients with metastatic disease, and usually involves the large vessels. Although patients with IVT received anticoagulants for a shorter period than those with SVT, better venous rethrombosis-related outcomes were observed in patients with IVT. In light of our results, prospective controlled trials are required to better define optimal anticoagulant strategies in this setting.

acknowledgements

The preliminary results of this study were reported at the 2008 Annual Meeting of the American Society of Clinical Oncology (abstract number 20604).

funding

This study was supported in part by grants FIS PI070387 from the Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III, Spain.

disclosure

The authors declare no conflicts of interest.

references

1. Prandoni P, Falanga A, Piccioli P. Cancer and venous thromboembolism. Lancet Oncol 2005; 6: 401–410.
2. Falanga A, Zacharski L. Deep vein thrombosis in cancer: the scale of the problem and approaches to management. Ann Oncol 2006; 16: 696–701.
3. Hutten B, Prins M, Gent M et al. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000; 18: 3078–3083.
4. Lyman GH, Khorana AA, Falanga A et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007; 25: 5490–5505.
5. Streiff MB. Diagnosis and initial treatment of venous thromboembolism in patients with cancer. J Clin Oncol 2009; 27: 4889–4894.
6. Khorana AA. Cancer and thrombosis: implications of published guidelines for clinical practice. Ann Oncol 2009; 20: 1619–1630.
7. Cronin CG, Lohan DG, Keane M et al. Prevalence and significance of asymptomatic venous thromboembolic disease found on oncologic staging CT. AJR Am J Roentgenol 2007; 189: 162–170.

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8. Gladish GW, Choe DH, Marom EM et al. Incidental pulmonary emboli in oncology patients: prevalence, CT evaluation, and natural history. Radiology 2006; 240: 246–255.
9. Sebastian AJ, Paddon AJ. Clinically unsuspected pulmonary embolism-an important secondary finding in oncology CT. Clin Radiol 2006; 61: 81–85.
10. Monreal M, Leizorovicz A, Cohen AT et al. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2006; 4: 1950–1956.
11. Siragusa S, Arcara C, Malato A et al. Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients. Ann Oncol 2005; 16: 136–139.
12. Khorana AA, Francis CW, Culakova E et al. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 2005; 104: 2822–2829.
13. Imberti D, Agnelli G, Ageno W et al. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. Haematologica 2008; 93: 273–278.
14. Kearon C, Khan SR, Agnelli G et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008; 133: 454–545.
15. Centre for Evidence-Based Medicine de Oxford. Levels of Evidence and Grades of Recommendation. Oxford: Centre for Evidence-Based Medicine. http://www.cebm.net.
16. Klimpfinger M, Green FL, Hutten VP et al. TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumors/UICC, 4th edition (corrected 2nd ed). Berlin, Germany: Springer-Verlag 1999.
17. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990; 263: 2753–2759.
18. Büller HR, Agnelli G, Hull RD et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest 2004; 126: 401–428.
19. Lee AY, Levine MN, Baker RI et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349: 146–153.
20. Tapson VF. Acute pulmonary embolism. N Engl J Med 2008; 358: 1037–1052.
21. O'Connell CL, Boswell WD, Duddalwar V et al. Unsuspected pulmonary emboli in cancer patients: clinical correlates and relevance. J Clin Oncol 2006; 24: 4928–4932.
22. Desai SR. Unsuspected pulmonary embolism on CT scanning: yet another headache for clinicians? Thorax 2007; 62: 470–472.
23. Engelke C, Rummeny EJ, Marten K. Pulmonary embolism at multi-detector row CT of chest: one-year survival of treated and untreated patients. Radiology 2006; 239: 563–575.

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