Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry

Davide Imberti,[1] Giancarlo Agnelli,[2] Walter Ageno,[3] Marco Moia,[4] Gualtiero Palareti,[5] Riccardo Pistelli,[6] Romina Rossi,[2] and Melina Verso[2] *for the MASTER Investigators*

[1]Hospital of Piacenza, Piacenza; [2]University of Perugia, Perugia; [3]University of Insubria, Varese; [4]IRCCS Maggiore Hospital, Milan; [5]University of Bologna, Bologna; [6]Catholic University, Rome, Italy

Acknowledgments: the MASTER investigators wish to thank Sanofi-Aventis Pharmaceuticals, Italy for supporting this registry with an unrestricted educational grant and the Comunica & Comunica group for administrative and logistic support. We express our particular gratitude to Valeria Cantone, Alfredo Spreafico, and Albino Ventura.

Funding: the study was supported by an unrestricted educational grant from Sanofi-Aventis SpA, Milan, Italy.

Manuscript received May 23, 2007. Manuscript accepted October 17, 2007.

Correspondence:
Davide Imberti, Thrombosis Center Emergency Department, Piacenza Hospital, via Taverna 49, 29100 Piacenza, Italy.
E-mail: d.imberti@ausl.pc.it

ABSTRACT

Background
Clinical characteristics and management of acute deep vein thrombosis and pulmonary embolism (PE) have been reported to be different in patients with and without cancer. The aim of this paper was to provide information on clinical characteristics and management of acute venous thromboembolism in patients with cancer by means of a large prospective registry.

Design and Methods
MASTER is a multicenter registry of consecutively recruited patients with symptomatic, objectively confirmed, acute venous thromboembolism. Information about clinical characteristics and management was collected by an electronic data network at the time of the index event.

Results
A total of 2119 patients were enrolled, of whom 424 (20%) had cancer. The incidence of bilateral lower limb deep vein thrombosis was significantly higher in patients with cancer than in patients without cancer (8.5% versus 4.6%; $p<0.01$), as were the rates of iliocaval thombosis (22.6% versus 14%; $p<0.001$), and upper limb deep vein thrombosis (9.9% versus 4.8%; $p<0.001$). Major bleeding (3.3% versus 1.1%; $p=0.001$), in-hospital treatment (73.3% versus 66.6%; $p=0.02$) and inferior vena cava filter implantation (7.3% versus 4.1%; $p=0.005$) were significantly more frequent in patients with cancer, in whom oral anticoagulants were less often used (64.2% versus 82%; $p<0.0001$).

Conclusions
The clinical presentation of acute venous thromboembolism is different and often more extensive in cancer patients than in patients free from malignancy. Moreover, the management of the acute phase of venous thromboembolism is more problematic in cancer patients, especially because of a higher rate of major bleeding and the need for implantation of inferior vena cava filters.

Key words: venous thrombosis, pulmonary embolism, cancer.

Citation: Imberti D, Agnelli G, Ageno W, Moia M, Palareti G, Pistelli R, Rossi R, and Verso M for the MASTERS Investigators. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. Haematologica 2008 Feb; 93(2):273-278. DOI: 10.3324/haematol.11458

Introduction

Recent studies have shown that cancer increases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) by four to six-fold and patients with malignancy represent about 15-20% of all patients with acute venous thromboembolism (VTE).[1-3] Furthermore, about 10% of patients presenting with unprovoked or idiopathic VTE are diagnosed with early or advanced malignancy within 2 years of the thrombotic event;[4,5] hence, approximately one quarter of all VTE cases are related to an underlying malignancy. The clinical characteristics of acute DVT and PE have been reported to be different in cancer patients compared to those in patients without cancer;[5] the natural history of VTE is usually more aggressive in oncologic patients and the probability of death in cancer patients with VTE is higher than that in patients with cancer alone or VTE alone.[6] Moreover, anticoagulant treatment failure is more frequent in patients with malignancy; a number of recent studies have clearly shown that the risk of recurrences is about two to three-fold higher and the risk of major bleeds two to six-fold higher in patients with cancer than in those without.[7-9] However, the clinical findings and management of acute VTE in patients with cancer have been previously described mainly in selected patients enrolled in cohort studies and randomized clinical trials. Therefore, data obtained from unselected populations fully representative of the real-world situation in this clinical setting are lacking.

The Multicenter Advanced Study for a Thromboembolism Registry (MASTER) is an Italian, multicenter, observational study aimed at prospectively collecting information on VTE patients and treatment practices.[10] A total of 25 hospitals were involved in the registry, quite equally distributed in three different regional areas (ten in northern Italy, five in central Italy and ten in southern Italy); nine were teaching hospitals, while the remaining 16 were secondary-care hospitals. Consecutive patients with objectively documented symptomatic VTE were enrolled between January 2002 and October 2004 and followed up for a total of 2 years.

The aim of this study was to compare the clinical characteristics and the management of acute VTE in a large cohort of patients with and without cancer.

Design and Methods

Inclusion criteria

To be enrolled in the observational registry, consecutive patients with symptomatic acute VTE had to have met the following criteria: 18 years of age or older, presence of objectively documented symptomatic DVT or PE, and potential availability for a long-term follow-up (life expectancy of more than 3 months and possibility of follow-up visits). All enrolled patients provided written informed consent.

Data collection

Information was collected in an electronic data network at the time of the index event. At each registry hospital data were collected by a designated study co-ordinator in the electronic case report form and submitted to a data management center through a secure website. Patients' identities remained as confidential information at the participating hospitals. Patients were identified through a number assigned by the study physician at each center. All confidential data were protected by passwords for electronic data and by storing all paper charts in secure facilities at the participating hospitals.

Study end-points

The following information was collected for the purposes of this study: baseline characteristics; site of thrombosis (proximal deep veins of lower limbs, distal deep veins of lower limbs, deep veins of the upper limbs, caval veins, pulmonary arteries); objective testing (compression ultrasonography, computed tomography scan, venography to diagnose DVT; computed tomography, ventilation/perfusion scan, perfusion scan, angiography to diagnose PE); presence of cancer at the time of VTE diagnosis (known or newly diagnosed); presence of temporary risk factors at the time of VTE diagnosis (recent surgery, recent trauma, severe medical diseases, immobilization, pregnancy, puerperium, oral contraceptives, central venous catheters); ongoing prophylaxis for VTE at the time of diagnosis; antithrombotic treatment during the acute phase of VTE (pharmacological therapy, inferior vena cava filter implantation); treatment-associated bleeding complications and setting of acute treatment of VTE (home-treatment, in-hospital treatment). Major and minor bleeds were defined according to criteria used in safety assessment in clinical trials. The study protocol did not dictate any interference with patient management. The choice of diagnostic methods and treatment of the VTE event were left to the attending physicians in the participating centers.

Statistical analysis

Baseline characteristics are reported by descriptive analysis. The χ^2 test was used to analyze the difference in frequencies in the two-way tables. Results are expressed as odds ratio (OR) and 95% confidence intervals (CI) where appropriate. Analysis of variance (ANOVA) was used to analyze the difference of means of continuous variables. Logistic regression analysis was performed to adjust for potential confounding variables. The Epi Info package 3.3.2 (Center for Disease Control and Prevention, Atlanta, USA) was used for all analyses.

Results

From January 2002 to October 2004 a total of 2119 consecutive patients (1056 males) were enrolled in the registry; of these, 424 (20.4%) had cancer. The baseline characteristics of these subjects are reported in Table 1. Known cancer was present in 374 patients (18%) and in 50 additional patients (2.4%) cancer was diagnosed at the time of VTE event. In seven patients (1.8%) with known cancer, a second malignancy was diagnosed. The sites of cancer are summarized in Table 2.

The mean age at the time of the VTE event was 59.3 ±18.1 years (range 18-99), with a difference between patients with and without cancer (65.7±13.6 and 57.6± 19.1, respectively; $p<0.0001$).

In 955 patients (45.1%) at least one temporary risk factor for VTE was observed and at the time of the index event pharmacological prophylaxis of VTE was in use in 387 patients (18.3%). Neither the presence of transient risk factors for VTE (Table 1) nor the use of ongoing thromboprophylaxis at the time of the diagnosis of VTE differed between the groups of patients with and without cancer (Table 3). The clinical presentations of acute VTE and the site distribution of DVT are summarized in Table 3 and Table 4, respectively. Of interest, the rates of PE (alone or associated with DVT) and of symptomatic proximal DVT were similar in patients with and without cancer. Conversely, the incidence of symptomatic bilateral lower limb DVT was significantly higher in patients with cancer than in patients free from malignancy (8.5% versus 4.6%; $p<0.01$), as were the rates of symptomatic iliocaval thombosis (22.6% versus 14%; $p<0.001$) and upper limb DVT (9.9% versus 4.8%; $p<0.001$) (Table 4).

Ninety percent of the patients received anticoagulant therapy for the acute treatment of VTE. The agents used were low-molecular-weight heparin (LMWH) in 79.5% of cases, unfractioned heparin (UFH) in 20.5% of cases and thrombolytics in 2.9% of cases; no difference was observed regarding the frequency of use of these antithrombotic drugs between cancer and non-cancer patients. By contrast, vena cava filters were positioned in more patients with malignancy than in patients without malignancy (7.3% versus 4.1%, respectively; $p=0.005$).

Six-hundred and seventy-six patients (35.1%) were entirely treated at home for VTE; the rate of in-hospital treatment was significantly higher in cancer patients than in those without cancer (73.3% versus 66.2%, respectively; $p=0.02$).

During the acute treatment of VTE, hemorrhagic complications occurred in 114 patients (5.4%); major bleeding was significantly more common in patients with cancer than in those without (3.3% versus 1.1%, respectively; $p=0.001$).

Finally, long-term treatment with oral anticoagulants was prescribed in 1662 patients (78.4%); in comparison with patients free from malignancy, oral anticoagulants were less frequently used in cancer patients (64.2% versus 82%, respectively; $p<0.0001$), in whom LMWH were significantly more often prescribed (30.4% versus 14.7%, respectively; $p<0.0001$).

Table 1. Baseline characteristics of patients with and without cancer at enrollment.

	With cancer (n=424)	*Without cancer (n=1695)*	*OR (95% CI)*	*p-value*
Gender				
Males	216 (50.9%)	840 (49.6%)		
Permanent risk factors for VTE				
Known thrombophilia*	5 (1.2%)	79 (4.7%)	0.30 (0.12-0.75)	< 0.01
FV Leiden	2 (0.5%)	20 (1.2%)	0.50 (0.11-2.21)	ns
Prothrombin G20210A	1 (0.2%)	19 (1.1%)	0.24 (0.03-1.80)	ns
PC deficiency	0 (0%)	7 (1.4%)	NA	
PS deficiency	0 (0%)	10 (0.6%)	NA	
APLA		0 (0%)	7 (1.4%)	NA
Hyperhomocysteinemia	1 (0.2%)	19 (1.1%)	0.23 (0.03-1.79)	ns
Previous DVT or PE	53 (12.5%)	258 (15.2%)	0.72 (0.52-0.99)	ns
Transient risk factors for VTE	168 (39.6%)	731 (43.1%)	1.00 (0.80-1.26)	ns
Recent immobilization (> 4 days)	58 (13.7%)	260 (15.3%)	0.77 (0.56-1.06)	ns
Surgery	86 (20.3%)	220 (13.0%)	1.63 (1.23-2.17)	< 0.001
Trauma	6 (1.4%)	196 (11.6%)	0.12 (0.05, 0.28)	< 0.001
Severe medical disease	54 (12.7%)	120 (7.1%)	1.65 (1-17-2.34)	< 0.01
Oral contraceptives	4 (0.9%)	110 (6.5%)	0.24 (0.08, 0.70)	< 0.01
Pregnancy/puerperium	0 (0%)	30 (1.8%)	NA	
Central vein catheter	3 (0.7%)	2 (0.1%)	18.27 (1.95, 171.17)	<0.05

*OR: odds ratio adjusted for gender, age and in-hospital treatment; CI: confidence interval; VTE: venous thromboembolism; AT: antithrombin; PC: protein C; PS: protein S; APLA: antiphospholipid antibodies; NA: not available for lack of convergence of the model. *Only known thrombophilia at enrollment is reported, since the design of the study did not include systematic screening for thrombophilia.*

Discussion

The data from this large Italian registry demonstrate that there are significant differences in the clinical characteristics of VTE between patients with and without cancer. Furthermore, the management of the acute phase of VTE is more complicated in oncologic patients, in terms of the incidence of major bleeds and need for implantation of IVC filters.

About 20% of the patients in the registry had cancer, either known to be present before enrollment or diagnosed at the time of the VTE event; this rate is comparable to that reported from several randomized clinical trials of VTE treatment[11] or prospective registries.[3] The most common tumor types found in our series were cancers of the gastrointestinal and genitourinary tracts, lung and breast; this reflects the high prevalence of these cancers in the general population and confirms previous published data.[12] Interestingly, data from a very large number of patients demonstrate a strong relationship between the location of DVT (iliaco-caval and bilateral) and cancer. In the past years very few studies have investigated possible associations between anatomic topography of DVT and malignancy. A retrospective small trial reported a 30% prevalence of malignancy in patients with idiopathic bilateral DVT,[13] while Bura and colleagues, in a prospective series of 100 patients, found that bilateral DVT was a significant risk indicator of malignancy and that cancer was present in 45% of such cases.[14] Recently, a prospective cohort study demonstrated that iliaco-caval and proximal locations of DVT were associated with a higher incidence of new cancer at 2 years of follow-up when compared to distal locations.[15]

Table 2. Sites of cancer.

	Known cancer	*Newly diagnosed cancer*	*Number of cancer*
Central nervous system	27	1	28
Hematologic	66	10	76*
Gastrointestinal	79	13	92*
Genito-urinary	101	15	116*
Lung	32	8	40
Breast	58	3	61
Melanoma	7	0	7
Sarcoma	4	0	4
Undefined	18	3	21*
Total	392	53	445§

**One patient had both an old and a new type of cancer affecting the same organ. §Eleven patients had two organs affected by cancer and three patients had three organs affected by cancer. Overall, 424 patients were affected by at least one malignancy.*

Table 3. Clinical characteristics and management of patients with and without cancer.

	With cancer (n=424)	*Without cancer (n=1695)*	*OR (95% CI)*	*p-value*
Primary prophylaxis of VTE	69 (16.3%)	318 (18.8%)	0.84 (0.62, 1.13)	ns
Clinical location				
PE (alone or associated with DVT)	109 (25.7%)	469 (27.7%)	0.90 (0.70, 1.16)	ns
DVT	315 (74.3%)	1226 (72.3%)	1.11 (0.86, 1.42)	ns
Initial therapy				
UFH	81 (19.1%)	351 (20.7%)	0.90 (0.68, 1.20)	ns
LMWH	312 (73.6%)	1161 (68.5%)	1.28 (1.00, 1.64)	ns
Thrombolysis	8 (1.9%)	54 (3.2%)	0.58 (0.25, 1.29)	ns
IVC filter	31 (7.3%)	70 (4.1%)	1.83 (1.15, 2.90)	0.005
In-hospital treatment	311(73.3%)	1132 (66.8%)	1.37 (1.07, 1.759	0.02
Long term therapy				
Oral anticoagulation	272 (64.2%)	1390 (82%)	0.39 (0.31, 0.50)	<0.0001
LMWH	129 (30.4%)	250 (14.7%)	2.53 (1.96, 3.27)	<0.0001
Bleeding complications				
Any bleeding	28 (6.6%)	47 (2.8%)	2.48 (1.48, 4.13)	0.0001
Major bleeding	14 (3.3%)	19 (1.1%)	3.01 (1.41, 6.40)	0.001

DVT: deep vein thrombosis; VTE: venous thromboembolism; PE: pulmonary embolism; IVC: inferior vena cava; LMWH: low-molecular weight heparin; UFH: unfractioned heparin; OR: odds ratio; CI: confidence interval; ns: not significant.

Table 4. Site distribution of deep vein thrombosis in patients with and without cancer.

	With cancer (n=424)	*Without cancer (n=1695)*	*OR (95% CI)*	*p-value*
Bilateral DVT	36 (8.5%)	78 (4.6%)	1.76 (1.15-2.69)	<0.01
Proximal DVT	324 (76.4%)	1278 (75.4%)	0.96 (0.79-1.30)	ns
Iliocaval DVT	96 (22.6%)	237 (14.0%)	2.02 (1.53-2.57)	<0.001
Upper limb DVT	42 (9.9%)	82 (4.8%)	2.16 (1,43-3.26)	<0.001

DVT: deep vein thrombosis; OR: odds ratio adjusted for age, gender and in-hospital treatment; CI: confidence interval.

The incidence of upper limb DVT was about two times higher in our patients with cancer than in those without; this difference was mainly due the presence of a central venous catheter (CVC) and is consistent with the figures reported in the literature.[16-18]

As expected, the rate of implantation of IVC filters was about two times higher in patients with malignancy. As a matter of fact, patients with cancer have contraindications to anticoagulant treatment and VTE recurrences, despite adequate anticoagulation, occur much more frequently in these patients than in patients free from malignancy; in these patients the recommended therapeutic approach is the placement of an IVC filter.[19] Moreover, in a large number of patients with acute VTE enrolled in a Spanish registry who were managed without the insertion of a IVC filter despite recent major bleeding, the mortality rate due to fatal hemorrhages or fatal PE in patients with cancer was about ten times higher than that observed in patients without malignancy.[20]

In the patients enrolled in our registry, the presence of a malignancy led physicians to treat the acute phase of VTE significantly more frequently in hospital; this finding confirms the results of the results of two recent clinical studie recent clinical studies, one prospective, the other retrospective. The prospective clinical trial showed that cancer was the most common reason for in-hospital treatment; nevertheless, more than half of the patients with known cancer were safely and effectively treated at home.[21] In a large retrospective cohort study, Ageno *et al*. recruited 321 cancer patients and demonstrated that home treatment of DVT was safe and feasible in almost two-thirds of cases.[22] We found that during the initial treatment of VTE, major bleeds occurred more frequently in cancer patients than in patients free from malignancy. Although the high risk of serious bleeding during prolonged treatment of VTE in oncologic patients is well known,[7-9] our data are peculiar and quite interesting; in fact, to our knowledge, there is no published information on bleeding complications during the acute phase of anticoagulation in a series of patients with cancer.

Finally, in our study oral anticoagulants were significantly less frequently used for long-term treatment in patients with cancer, in whom LMWH were more often prescribed. These results are not surprising for several reasons. Several studies demonstrated that during secondary VTE prophylaxis with oral anticoagulants, cancer patients are at increased risk of both recurrent VTE and major bleeding compared to patients without cancer;[9] moreover, there are several limitations to the use of warfarin in the oncologic population (drug interactions, malnutrition, liver dysfunction, gastrointestinal disturbances, dose adjustment). However, there is strong evidence that long-term LMWH prophylaxis is efficacious and safe for preventing VTE in cancer patients[23-25] and the latest American College of Chest Physicians guidelines recommended treatment with LMWH for 3 to 6 months for the prevention of recurrent thrombosis for the majority of patients with DVT and cancer.[19]

Our study has some limitations. First, one of the inclusion criteria of this registry was the potential availability of patients with VTE for a long-term follow-up. Thus, a number of patients with a poor prognosis following the acute event, such as patients with massive PE or patients with advanced stage cancer were excluded. However, such patients represent a minority of patients with VTE and it is unlikely that their inclusion would have substantially modified our results. Second, we did not conduct systematic screening for the detection of occult cancer in patients with acute idiopathic VTE; thus it is possible that the incidence of cancer-associated VTE was slightly under-estimated, leading to a potential bias. However, this limitation is entirely due to the design of the study; in fact, in contrast to a randomized clinical trial, no experimental intervention is imposed in a registry survey and the management is determined only by the treating physicians. Third, the number of bilateral and iliocaval DVT must be considered cautiously; in fact it is probably an underestimate, since a systematic search for asymptomatic contralateral or iliocaval extension was not performed in patients entering the register with a diagnosis of proximal DVT. In conclusion, our study demonstrates that in a real-world situation the clinical presentation of acute VTE in an unselected population is different and often more extensive in patients with cancer than in those without. Moreover, the management of the acute phase of VTE is more problematic in cancer patients because of a higher rate of major hemorrhages and the need for implantation of IVC filters. Based on the results of our study, specific strategies for the management of acute VTE in cancer patients seem to be warranted.

Appendix: Participating investigators and study sites

Study Coordinator: G. Agnelli, Azienda Ospedaliera di Perugia, Perugia.

Investigators: W. Ageno and J. Vitale, Ospedale di Circolo Macchi, Varese; M. Bellisi, Policlinico "Paolo Giaccone", Palermo; M. Bianchi, Ospedale Valduce, Como; V. Brancaccio, Ospedale Cardarelli, Napoli; A. Ciampa, Azienda Ospedaliera San Giovanni Moscati, Avellino; C. Cimminiello, Ospedale Civile di Vimercate, Vimercate (MI); A. Dragani, Ospedale Civile di Pescara, Pescara; S. Grifoni, Azienda Ospedaliera Careggi, Firenze; D. Imberti, Ospedale Civile di Piacenza, Piacenza; M. Impagliatelli, IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (FG); G. Iovane, ASL Bianchi Melacrino-Morelli,, Reggio Calabria; R. Margheriti, Ospedale G.B. Grassi, Ostia Lido (RM); M. Moia, Ospedale Maggiore di Milano, Milano; A. Musumeci, Ospedale Vittorio Emanuele II, Catania; G. Palareti, Policlinico S. Orsola Malpigli, Bologna; M. Pini,

Ospedale Civile di Fidenza, Fidenza (PR); P.A.. Pittaluga, Ospedale Galliera, Genova; V. Prisco, Ospedale ASL SA/2, Mercato San Severino (SA); S. Rupoli, Ospedale Regionale Torrette, Torrette di Ancona (AN); G. Scannapieco, Ospedale Civile Ca' Foncello, Treviso; S. Signorelli, Ospedale Garibaldi, Catania; M. Silingardi, Azienda Ospedaliera S. Maria Nuova, Reggio Emilia; S. Siragusa, Policlinico "Paolo Giaccone", Palermo; V. Virgilio, Ospedale Garibaldi, Catania.

The authors reported no potential conflicts of interest.

References

1. White RH. The epidemiology of venous thromboembolism. Circulation 2003;107:I4-8.
2. Ageno W, Squizzato A, Garcia D, Imberti D. Epidemiology and risk factors of venous thromboembolism. Semin Thromb Hemost 2006;32:651-8.
3. Monreal M, Falgà C, Valdes M, Suarez C, Gabriel F, Tolosa C, et al. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE Registry. The RIETE Investigators. J Thromb Haemost 2006;4:1950-6.
4. Prandoni P, Lensing AW, Buller HR, Cogo A, Prins MH, Cattelan AM, et al. Deep vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 1992; 327:1128-33.
5. Lee A, Levine M. Venous thromboembolism and cancer: risk and outcomes. Circulation 2003;107: 117-21.
6. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine 1999;78:285-91.
7. Palareti G, Legnani C, Lee A, Manotti A, Hirsh J, D'Angelo A, et al. A comparison of the safety and efficacy of oral anticoagulant for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost 2000;84:805-10.
8. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. 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: 3078-83.
9. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-8.
10. Agnelli G, Ageno W, Caponi C, Imberti D, Moia M, Palareti G, et al. A prospective registry on the long-term clinical outcome of venous thromboembolism: description of the study cohort. The MASTER Investigators. J Thromb Haemost 2005;3[suppl 1]:P1650.
11. Prandoni P. How I treat venous thromboembolism in patients with cancer. Blood 2005;106:4027-33.
12. Lee AY. Management of thrombosis in cancer: primary prevention and secondary prophylaxis. Br J Haematol 2005;128:291-302.
13. Rance A, Emmerich J, Guedy C, Fiessinger JN. Occult cancer in patients with bilateral deep vein thrombosis. Lancet 1997;350:1448-9.
14. Bura A, Cailleaux N, Bienvenu B, Leger P, Bissery A, Boccalon H, et al. Incidence and prognosis of cancer associated with bilateral venous thrombosis: a prospective study of 103 patients. J Thromb Haemost 2004;2:441-4.
15. Seinturier C, Bosson J, Colonna M, Imbert B, Carpentier P. Site and clinical outcome of deep vein thrombosis of the lower limb: an epidemiological study. J Thromb Haemost 2005;3:1362-7.
16. Prandoni P, Polistena P, Bernardi E, Cogo A, Casara D, Verlato F, et al. Upper extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med 1997;157:57-62.
17. Karabay O, Yetkin U, Onol H. Upper extremities deep vein thrombosis: clinical and treatment characteristics. Int Med Res 2004;32:429-35.
18. Savage KJ, Wells PS, Schulz V, Goudie D, Morrow B, Cruickshank M. Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremities. Thromb Haemost 1999;82:1008-10.
19. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease. Chest 2004;126 [suppl 3]:401S-28S.
20. Nieto JA, De Tuesta AD, Marchena PJ, Monreal M. Clinical outcome of patients with venous thromboembolism and recent major bleedings: findings from a prospective registry (RIETE). J Thromb Haemost 2005; 3:703-9.
21. Ageno W, Grimwood R, Limbiati S, Dentali F, Steidl L, Wells PS. Home-treatment of deep vein thrombosis in patients with cancer. Haematologica 2005;90:220-4.
22. Ageno W, Steidl L, Marchesi C, Dentali F, Mera V, Squizzato A, et al. Selecting patients for home treatment of deep vein thrombosis: the problem of cancer. Haematologica 2002;87:286-91.
23. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins MH. Low-molecular-weight heparin versus coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-53.
24. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 2002;162: 1729-35.
25. Hull R, Pineo G, Brant R, Mah A, Burke N, Dear R, et al. Long term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. The LITE Investigators. Am J Med 2006;119:1062-72.