with obliterative atherosclerosis. Thromb Res 1988;51:575-81.
9. Lapolla A, Piarulli F, Sartore G, Rossetti C, Martano L, Carraro P, et al. Peripheral artery disease in type 2 diabetes: the role of fibrinolysis. Thromb Haemost 2003;89:91-6.
10. Boneu B, Leger P, Arnaud C. Haemostatic system activation and prediction of vascular events in patients presenting with stable peripheral arterial disease of moderate severity. Royal Study Group. Blood Coagul Fibrinol 1998;9:129-35.
11. Philipp CS, Cisar LA, Kim HC, Wilson AC, Saidi P, Kostis JB. Association of hemostatic factors with peripheral vascular disease. Am Heart J 1997;134:978-84.
12. Kalaria VG, Zareba W, Moss AJ, Pancio G, Marder VJ, Morrissey JH, et al. Gender-related differences in thrombogenic factors predicting recurrent cardiac events in patients after acute myocardial infarction. Am J Cardiol 2000;85: 1401-8.

Recurrent thromboembolism and major bleeding during oral anticoagulant therapy in patients with solid cancer: findings from the RIETE registry

Following an episode of venous thromboembolism (VTE), the risk of recurrent VTE and major bleeding complications during oral anticoagulant therapy with vitamin K antagonists (VKA) in cancer patients exceeds that observed in patients free from malignancy.[1-3] According to the results of several randomized clinical trials,[4-7] international guidelines recommend the use of sub-therapeutic doses of low-molecular-weight heparins (LMWH) for the long-term prevention of recurrent VTE in all cancer patients.[8-10] However, in clinical practice many clinicians still administer VKA to their cancer patients, especially to those with limited disease and longer life expectancy.

We determined the risk of recurrent VTE and major bleeding in a wide number of patients with and without cancer who were recruited in the international RIETE registry, had an initial treatment with (LMW)heparin overlapped by VKA (targeting an International Normalized Ratio [INR] between 2.0 and 3.0), and then had a 3-month follow-up.

Between March 2001 and May 2007, 18,883 consecutive patients with symptomatic, acute DVT or PE, as confirmed by objective tests were enrolled in the RIETE registry, and were, therefore, eligible for our investigation. Of these patients, 6,139 were excluded: 4,999 (of whom 1,496-29.9% - affected by cancer) because of treatment with antithrombotic drugs other than VKA, 838 because of lack of long-term antithrombotic treatment, 223 because of the development of manifest cancer during the 3-month follow-up period, and 79 because of hematologic malignancies. Of the remaining 12,744 patients, 11,365 were free from malignancy, 407 had cancer with distant metastases, and 972 had a more limited cancer disease. The incidence of recurrent VTE and major bleeding was calculated for patients with and without cancer, and then separately for cancer patients with and without distant metastases. The diagnosis of recurrent VTE and major bleeding was carried out according to widely accepted methods and criteria that have been extensively described elsewhere.[11,12] Odds ratios (OR) and their 95% confidence intervals (CI) were calculated for the clinical characteristics and the 3-month outcome for patients without malignancy in comparison to the whole group of cancer patients, and separately for those with and without distant metastases. Dichotomous variables were tested with χ^2 test and continuous variables with Student's t-test. In order to measure predictors of 3-month recurrent VTE and major bleeding, a multivariate analysis was carried out using a Cox proportional hazard analysis after adjusting for age, sex, and modality of clinical presentation (symptomatic DVT alone or symptomatic PE with or without DVT). Statistical analyses were conducted with SPSS for Windows Release 13.0 and Epidat 3.1.

Table 1 shows the main demographic and clinical characteristics of the study patients, separately for those without malignancy, cancer patients with distant metastases, and cancer patients with more limited disease. During the study period, 333 patients died: 189 (1.7%) belonging to the first group, 103 (25.3%) to the second group, and 41 (4.2%) to the third. During the first three months of VKA treatment, recurrent VTE developed in 154 patients without malignancy (1.4%, fatal in 16), in 27 cancer patients with distant metastases (6.6%, fatal in 3), and in 31 cancer patients with more limited disease (3.2%, fatal in 4). In comparison to patients without malignancy, the OR of recurrent VTE in the whole group of cancer patients was 3.2 (95% CI, 2.4-4.3), and in cancer patients with and without distant metastases was 5.2

Table 1. Main demographic and clinical characteristics of the study patients.

	No cancer	*Cancer without metastases*	*Cancer with metastases*	*OR (95% CI) cancer without metastases vs. no cancer*	*OR (95% CI) cancer with metastases vs. no cancer*
Patients, N	11365	972	407		
Clinical characteristics					
Gender (males)	5698 (50%)	553 (57%)	223 (55%)	1.3 (1.2-1.5)†	1.2 (1.0-1.5)
Body weight <65 kg	2500 (22%)	242 (25%)	127 (31%)	1.2 (1.0-1.4)†	1.6 (1.3-2.0)†
Age (mean, SD)	64.7 (17.3)	71.0 (11.6)†	67.7 (12.2)†	–	–
Risk factors for VTE					
Surgery	1292 (11%)	210 (22%)	42 (10%)	2.1 (1.8-2.5)†	0.9 (0.6-1.2)
Immobility ≥4 days	2629 (23%)	158 (16%)	61 (15%)	0.6 (0.5-0.8)†	0.6 (0.4-0.8)
Prior VTE	1950 (17%)	174 (18%)	73 (18%)	1.1 (0.9-1.2)	1.1 (0.8-1.4)
VTE characteristics					
Clinically overt PE	5217 (46%)	473 (49%)	165 (41%)	1.1 (1.0-1.3)	0.8 (0.7-0.9)†
Cancer characteristics					
Cancer >3 months earlier	-	702 (72%)	254 (62%)	–	–
Site of cancer,	–				
Lung		48 (4.9%)	59 (15%)	–	–
Breast		189 (19%)	56 (14%)	–	–
Gastrointestinal		188 (19%)	96 (24%)	–	–
Pancreas		4 (0.4%)	20 (4.9%)	–	–
Genitourinary		392 (40%)	125 (31%)	–	–
Cerebral		57 (5.9%)	6 (1.5%)	–	–
Other		94 (9.7%)	45 (11%)	–	–
Treatment					
Initial therapy, LMWH	10144 (89%)	875 (90%)	361 (89%)	1.1 (0.9-1.4)	0.9 (0.7-1.3)
Initial therapy, UFH	1053 (9.3%)	80 (8.2%)	39 (9.6%)	0.9 (0.7-1.1)	1.0 (0.7-1.5)
Inferior vena cava filter	117 (1.0%)	26 (2.7%)	14 (3.4%)	2.6 (1.7-4.1)†	3.4 (1.9-6.0)†

†*statistically significant.*

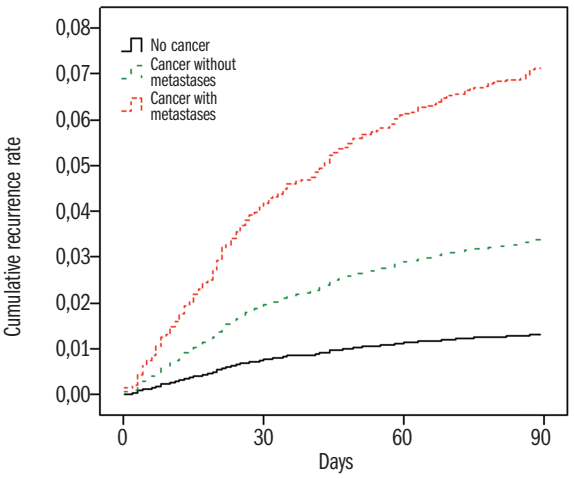

Figure 1. Cumulative incidence of recurrent venous thromboembolism in patients without malignancy and in cancer patients with and without distant metastases.

(3.4-7.9) and 2.4 (1.6-3.5) respectively. The corresponding figures for the adjusted hazard ratio (HR) were 3.5 (95% CI, 2.5-4.7), 5.6 (3.7-8.4), and 2.6 (1.8 to 3.8) respectively (Figure 1). During the first three months of VKA treatment, major bleeding developed in 150 patients without malignancy (1.3%, fatal in 19), in 20 cancer patients with distant metastases (4.9%, fatal in 7), and in 16 cancer patients with more limited disease (1.9%, fatal in 4). In comparison to patients without malignancy, the OR of major bleeding in the whole group of cancer patients was 2.0 (95% CI, 1.4-2.9), and in cancer patients with and without metastases was 3.9 (2.4-6.2) and 1.3 (0.7-2.1) respectively. The corresponding figures for the adjusted HR were 1.8 (95% CI, 1.2-2.6) 3.9 (2.4-6.2) and 1.1 (0.6-1.8) respectively.

Our enquiry presents several limitations. Indeed, a relevant number of patients (of whom almost 30% were affected by cancer) had an anticoagulant treatment other than VKA, and, therefore, did not qualify for the study. Data concerning the diagnosis of cancer, disease stage, recurrent VTE, and major bleeding were accepted on assessments made at each participating center, and could not be confirmed by an independent adjudication committee. Finally, information on the quality of anticoagulation achieved during the treatment with VKA was not available.

In spite of these limitations, the results of our investigation fully confirm that cancer patients with VTE have an overall risk of recurrent VTE and major bleeding complications during VKA that exceeds that expected in patients free from malignancy.[1-3] However, in the subgroup of cancer patients with more limited disease the rate of major bleeding does not differ from that expected in cancer free patients. Whether these patients may benefit from more intense regimens of VKA as an alternative to LMWH is worthy of further investigation.

*Paolo Prandoni,[1] Javier Trujillo-Santos,[2] Teresa Surico,[1] Fabio Dalla Valle,[1] Andrea Piccioli,[1] and Manuel Monreal[3] for the RIETE Investigators**

[1]Department of Medical and Surgical Sciences, University of Padua, Italy; [2]Department of Internal Medicine, Hospital Santa María de Rosell, Cartagena, Murcia, Spain; [3]Department of Internal Medicine, Hospital Germans Trias i Pujol, Badalona, Spain

**RIETE Registry. Coordinator: Monreal M. Steering Committee: Decousus H, Prandoni P, Brenner B. National Coordinators: Barba R (Spain), Di Micco P (Italy), Guillot K (France). Coordinating Center: S & H Medical Science Service. Members: Alcalde M, Arcelus JI, Ballaz A, Barba R, Blanco A, Barrón M, Casado I, Cañas I, Cisneros E, Conget F, De Zárraga M, Fernández-Capitán C, Font Ll, Gallego P, García-Bragado F, Gutiérrez J, Gutiérrez MR, Hermosa MJ, Hernández L, Herrera S, Jiménez D, Lecumberri R, León JM, López L, López I, Madridano O, Maestre A, Martín-Villasclaras JJ, Mejias I, Monreal M, Naufall MD, Nieto JA, Oribe M, Orue MT, Otero R, Rabuñal R, Rodríguez C, Rosa V, Ruiz-Giménez N, Ruiz-Ribó MD, Sahuquillo JC, Sampériz AL, Sánchez JF, Sánchez R, Soler S, Soto MJ, Tirado R, Todolí JA, Tolosa C, Trujillo J, Valdés M, Valdés V, Valle R, Vela J (Spain); Mismetti P, Rivron-Guillot K, Boccalon H, Le Corvoisier P, Quere I (France); Di Micco P, Duce R, Enea I, Poggio R, Prandoni P, Schenone A, Tiraferri E (Italy).*

Acknowledgments: we express our gratitude to Sanofi-Aventis Spain for supporting this Registry with an unrestricted educational grant and the Registry Coordinating Center, S & H Medical Science Service, for their logistic and administrative support.

Funding: the project has been partially supported by Red Respira from the Instituto Carlos III (RedRespira-ISCiii-RTIC-03/11).

Correspondence: Paolo Prandoni, Dipartimento di Scienze Mediche e Chirurgiche, Clinica Medica II, Università di Padova. E-mail: paoloprandoni@tin.it

Citation: Prandoni P, Trujillo-Santos J, Surico T, Dalla Valle F, Piccioli A, Monreal M for the RIETE Investigators. Recurrent thromboembolism and major bleeding during oral anticoagulant therapy in patients with solid cancer: findings from the RIETE registry. Haematologica 2008; 93:1432-1434. doi: 10.3324/haematol.13055

References

1. Prandoni P, Lensing AWA, 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.
2. Hutten B, Prins M, Gent M, Ginsberg J, Tijsen JGP, 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.
3. Palareti G, Legnani C, Agnes L, Manotti C, Hirsh J, D'Angelo A, et al. A comparison of the safety and efficacy of oral anticoagulation for the treatment of venous thromboembolic disease in patients with or without malignancy. Thromb Haemost 2000;84:805-10.
4. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, 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;349:146-53.
5. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer. Arch Intern Med 2002;162:1729-35.
6. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 2006;119:1062-72.
7. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost 2006;12:389-96.
8. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126:401-28S.
9. Nicolaides AN, Fareed J, Kakkar AK, Breddin HK, Goldhaber SZ, Hull R, et al. Prevention and treatment of venous thromboembolism. International Consensus

Statement. Guidelines according to scientific evidence. Int Angiol 2006;25:101-61.
10. Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, et al. American Society of Clinical Oncology Guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007;25:5490-505.
11. Arcelus JI, Monreal M, Caprini JA, Suárez C, González-Fajardo JA. The management and outcome of acute venous thromboembolism: a prospective registry including 4011 patients. J Vasc Surg 2003;38:916-22.
12. Monreal M, Falgá C, Valdés M, Suárez C, Gabriel F, Tolosa C, Montes J. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2006; 4:1950-6.

Enumeration of cytomegalovirus-specific interferonγ CD8⁺ and CD4⁺ T cells early after allogeneic stem cell transplantation may identify patients at risk of active cytomegalovirus infection

Recovery of functional cytomegalovirus (CMV)-specific T lymphocytes is critical for protection from active CMV infection and disease in allogeneic stem cell transplant recipients (Allo-SCT).[1-6] To date, assessment of CMV-specific T-cell immunity has not had a major impact on the clinical management of CMV infection in these patients, as no widely accepted thresholds in the number of CMV-specific T cells providing protection have been established. In the present study, we optimized a simple intracellular cytokine staining (ICS), and investigated whether enumeration of CMV-specific interferon (IFN)γ CD8⁺ and CD4⁺ T cells early after transplantation could reliably predict the development of active CMV infection within 100 days after transplantation. From January to October 2007, 36 patients undergoing Allo-SCT were included in the study. The study was approved by the Ethics Committees and written informed consent was obtained from all patients. Relevant clinical data of patients are summarized in Table 1. Patients were monitored for active CMV infection once or twice a week by pp65 antigenemia,[7] CMV DNAemia (CMV real-time PCR, Abbott Molecular, Des Plaines, IL, USA or AMPLICOR CMV Monitor, Roche Indianapolis, USA) or both. Pre-emptive therapy was initiated upon a positive antigenemia or 2 consecutive positive plasma PCRs, and discontinued upon two consecutive negative results as previously reported.[7] CMV pneumonitis was diagnosed and treated on the basis of established protocols.[7] Heparinized blood samples from patients were obtained at days +30 (median 34 days; range 30-53) and +60 (median 62 days; range 54 to 85 days). Blood samples were also obtained from healthy CMV-seropositive (n=7) and CMV-seronegative individuals (n=5). Enumeration of IFNγ CD8⁺ and CD4⁺ T cells was carried out by ICS (BD Fastimmune, BDBiosciences, San Josè, CA, USA) following the manufacturer's instructions. A set of overlapping peptides spanning the highly immunogenic pp65 and IE-1 CMV proteins, obtained from JPT peptide Technologies GmbH (Berlin, Germany), was chosen as the antigen (2 μg/peptide/mL).[8] Responses >0.1% were considered specific. Control samples and specimens from CMV-seronegative subjects yielded IFNγ responses <0.07%. IFNγ responses of CMV-seropositive individuals ranged from 0.20% to 5.5% (median 0.45% of IFNγ CD8⁺ T cells and 0.35% of IFNγ CD4⁺ T cells).

Fifteen patients (44%) experienced active CMV infection (11 D+/R+, 3 D-/R+ and 1 D+/R-), 8 before day +30 (median 19.5 days; range, 8-41 days) and 7 beyond day 30 (median 44.0 days; range 35-56 days). Twenty-one patients (18 D+/R+, 3 D-/R+) did not. Two patients died during the study period (one due to CMV pneumonitis on day +68, and the other due to a proven invasive pulmonary aspergillosis on day +25). Of the 28 patients free of active CMV infection at the first sampling time, IFNγ responses were detected in all but one patient. Individual data are shown in Figure 1. The median counts of either cell subset were significantly higher in patients not developing active CMV infection (1.69 cells/μL of CD8⁺ and 1.29 cells/μL of CD4⁺ T cells) than in those who experienced it later (0.32 cell/μL and 0.24 cell/μL respectively). A threshold in the number of either IFNγ subset predicting protection against active CMV infection was estab-

Table 1. Patients' characteristics.

Parameter	
Total n. of patients	36
Median age, yrs (range)	47 (22-69)
Sex, n. male patients/n. female patients	17/19
Diagnosis, n. patients (%)	
Acute myeloid leukemia	11 (30.6)
Acute lymphoblastic leukemia	1 (2.8)
Chronic myeloid leukemia	3 (8.3)
Idiopathic myelofibrosis	3 (8.3)
Myelodysplastic syndrome	2 (5.6)
Non-Hodgkin's lymphoma	9 (25)
Hodgkin's lymphoma	3 (8.3)
Multiple myeloma	3 (8.3)
Severe aplastic anemia	1 (2.8)
CMV serostatus[a], n. patients (%)	
D^+/R^+	29 (80.5)
D^-/R^+	6 (16.7)
D^+/R^-	1 (2.8).
Donor type, n. patients (%)	
HLA-identical sibling	21 (58.3)
Mismatched related donor	2 (5.6)
Matched unrelated donor	8 (22.2)
Mismatched unrelated donor	5 (13.9)
Conditioning regimen[b], n. patients (%)	
Non-myeloablative	25 (69.4)
Fludarabine plus Melphalan	17 (47.2)
Fludarabine plus Busulphan	8 (22.2)
Myeloablative	11 (30.6)
Busulphan plus Cyclophosphamide	6 (16.7)
TBI plus Cyclophosphamide	3 (8.3)
Fludarabine-Thiothepa-Busulphan-Thymoglobulin	2 (5.6)
Stem cell source	
Peripheral blood	33 (91.6)
Umbilical cord blood	2 (5.6)
Bone marrow	1 (2.8)
GvHD prophylaxis	
Cyclosporine A + Methotrexate	23 (63.9)
Cyclosporine A + MMF	11 (30.6)
Cyclosporine A + Prednisone	2 (5.6)
Acute GvHD incidence[c]	
Grades 0-I	23 (63.6)
Grades II-IV	13 (36.4)
Steroid therapy	
Yes	9 (25)
No	27 (75)

[a]Healthy individuals, donor and transplant recipient CMV-serostatus was determined by a commercial ELISA. [b]Incidence if occurring before the last time point evaluated (day +60). [c]For patients who received a graft from either an unrelated donor or a HLA-mismatched donor, rabbit antithymocyte globulin (ATG) (3-6 mg/kg) was added to reduced-intensity conditioning. TBI: total body irradiation.