Impact of chemotherapy on venous thromboembolism.
Comment to: Regional lymph node metastases are a strong risk factor for venous thromboembolism: results from the Vienna Cancer and Thrombosis Study

We read with great interest the paper by Dickmann and colleagues discussing the association of cancer-associated venous thromboembolism (VTE) and disease stage.[1] The concepts that cancer cells might engage the coagulation pathways and that thrombophilia might significantly contribute to cancer natural history, are increasingly recognized.[2,3] Some reports indicate that over 90% of cancer patients exhibit hemostatic abnormalities, whose incidence, nature, and degree widely vary depending on the type and the extent of tumor burden.[4-7]

In this context, we strongly agree with the Authors' perspective that metastatic cancer does represent a significant risk factor for VTE (due to increased tumor bulk and release of procoagulant factors from the tumor itself). Nonetheless, we must be cautious with the assertion that the presence of regional lymph-node metastases is predictive for increased VTE incidence. Indeed, as the Authors clearly acknowledge, the heterogeneity of the recruited population poses a serious limitation to their conclusions, as the relatively small number of patients/VTE events in each tumor type did not allow an association between stage and occurrence of VTE in single tumor sites to be analyzed. This latter approach was that followed by the Californian Cancer Registry (CCR) to investigate VTE incidence among patients with various common cancers[8] in which there were enough recruited subjects to confer sufficient power for a sub-group analysis.

Nonetheless, if we look in detail at the results of the CCR study, the incidence of VTE widely varied with cancer type and was highest among patients initially diagnosed with metastatic-stage disease. Conversely, not all regional-stage cancer types were associated with significant HRs for VTE occurrence. In our opinion, these results could be, at least partially, explained by the distribution of regional-stage among the various cancer types. Moreover, we must not forget the role that anti-cancer drugs may play as thrombotic triggers in association with specific stages of the disease. This is suggested by the findings that VTE risk in cancer patients increases in the first three months, peaks at six months, and starts declining during the first year after initial diagnosis, a trend that has been clearly correlated to the administration of combined anti-cancer therapies.[9-11] In this respect, it has recently been demonstrated that platinum compounds and/or gemcitabine are significantly associated with an increased risk of VTE.[9,12] Moreover, fluoropyrimidine-based regimens were shown to induce an acquired thrombophilic condition possibly responsible for VTE development during chemotherapy.[9]

Unfortunately, the lack of specific information on the staging of patients within the different groups of tumors in one study,[1] and the lack of identification of specific chemotherapeutic regimens in both,[1,8] do not allow a definitive conclusion to be drawn and prevent reproducibility of the results in different patient populations. Indeed, when we compared their findings with those obtained in our study cohort, significant differences were revealed. At the beginning of January 2007, the Medical Oncology Branch of Tor Vergata Clinical Center, Rome, Italy, started recruiting ambulatory patients with primary or relapsing/recurrent solid cancers. The study is being carried out with the approval of the appropriate Institutional ethics committee and in accordance with the principles embodied in the Declaration of Helsinki. These patients are prospectively followed to investigate possible predictors of cancer-associated VTE. At 31st December 2012, a total of 655 consecutive eligible patients (age 61±11 years, 323 males) had been enrolled. All patients were at the start of a new chemotherapy regimen (7% neoadjuvant, 32% adjuvant and 61% metastatic treatments) and 4% received concurrent radiotherapy. No patient received thromboprophylaxis. Inclusion and exclusion criteria had been previously reported.[9] All patients provided written informed

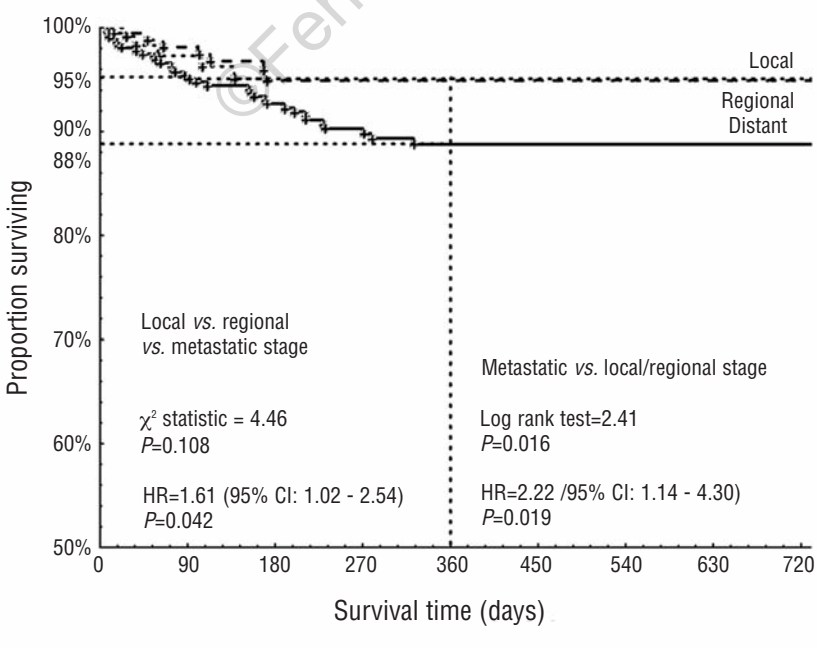

Figure 1. Kaplan-Meier analysis of VTE-free survival time in cancer patients categorized on the basis of disease stage. Dashed line: local stage; dotted line: regional stage; solid line: distant stage.

Table 1. Distribution analysis of anti-cancer drugs associated to hemostatic activation and/or increased VTE risk in different disease stages.

	Chemotherapy regimen including			
	Platinum	Gemcitabine	Fluoropyrimidine	Bevacizumab
Local, n = 117	59 (18%)	4 (5%)	68 (24%)	1 (1%)
Regional, n =174	99 (29%)	16 (18%)	81 (28%)	3 (3%)
Distant, n = 364	179 (53%)	68 (77%)*	136 (48%)*	89 (96%)*
Total treated	**337 (51%)**	**88 (13%)**	**285 (44%)**	**93 (14%)**

*χ^2 test for comparison: P< 0.001.

consent, and blood samples were drawn and collected in the facilities of the Inter-Institutional Multidisciplinary Biobank (BioBIM) of the IRCCS San Raffaele Pisana Hospital, Rome. Eighteen percent of patients had local, 27% regional and 55% distant stage. Disease prevalence and the chemotherapy drugs used were in the same ranges as previously reported.[9] Apart from a slightly higher prevalence of colorectal cancer (30%), the study cohort was comparable to that studied by Dickmann *et al.*[1]

Patients were followed-up for two years or until time of VTE diagnosis. Patients were seen regularly at their scheduled chemotherapy visits or at the occurrence of clinically suspected VTE. VTE occurred in 7% (17 pulmonary embolism and 28 deep venous thrombosis) of patients (median time-to-event: 3 months). Univariate Cox proportional hazards survival analysis showed that worsening tumor stage (from low to regional to distant stage) was weakly, but significantly associated to VTE incidence with a Hazard Ratio (HR) of 1.61 (95%CI: 1.02-2.54; *P*=0.042). However, this association was due to the presence of metastatic, but not regional disease, as clearly evident in the Kaplan-Meier analysis (Figure 1). Furthermore, the VTE predictive value of worsening stage was completely lost at multivariate analysis after adjustment for age, sex, site of primary disease, ECOG performance status, class of risk according to Khorana *et al.*,[13] and concurrent treatment with different supportive or anti-cancer drugs or bevacizumab.

As in the study by Dickmann *et al.*, the population analyzed was too small to answer any question concerning the pro-thrombotic role of chemotherapy, and similar limitations do apply. However, a cross-tabulation analysis of the use of platinum compounds, gemcitabine fluoropyrimidine, or bevacizumab (i.e. those drugs formerly implicated in hemostatic changes and cancer-related VTE) was performed to explore possible association with the disease stage. The results obtained indicate that a different combination of these drugs was mostly used in regional/distant stage cancer (Table 1).

As indicated above, these results are far from providing answers to the questions posed and, obviously, the same limitations raised for the study by Dickmann *et al.* remain.[1] Despite the presence of some information related to the use of anticancer drugs in our patient cohort, the low number of patients enrolled and the heterogeneity of the cases do not allow a subgroup analysis to be performed.

Moreover, single center recruitment might represent a further limitation as its primary and most obvious shortcoming is the potentially limited external validity. Nonetheless, we hope that open debate in this field of oncology might throw light on new perspectives and prompt new multi-center prospective studies. Such studies could provide specific answers to the doubts that remain and widen our knowledge about the pathophysiology of cancer-associated VTE.

Patrizia Ferroni,[1] Silvia Riondino,[1] Fiorella Guadagni,[1] and Mario Roselli[2]

[1]Department of Advanced Biotechnologies and Bioimaging, IRCCS San Raffaele Pisana, Rome; and [2]Department of Systems Medicine, Medical Oncology, Tor Vergata Clinical Center, University of Rome "Tor Vergata", Rome, Italy

Correspondence: patrizia.ferroni@sanraffaele.it

doi:10.3324/haematol.2013.092528

Key words: venous thromboembolism, disease stage, hemostatic activation.

Funding: this work has been partially supported by the Italian Ministry of Health Grant MERIT RBNE08NKH7.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Dickmann B, Ahlbrecht J, Ay C, Dunkler D, Thaler J, Scheithauer W, et al. Regional lymph node metastases are a strong risk factor for venous thromboembolism: results from the Vienna Cancer and Thrombosis Study. Haematologica. 2013;98(8):1309-14.
2. Rak J, Yu JL, Luyendyk J, Mackman N. Oncogenes, trousseau syndrome, and cancer-related changes in the coagulome of mice and humans. Cancer Res. 2006;66(22):10643-6.
3. Gil-Bernabé AM, Serena Lucotti S, Ruth J, Muschel RJ. Coagulation and metastasis: what does the experimental literature tell us? Br J Haematol. 2013;162(4):433-41.
4. Roselli M, Mineo TC, Basili S, Martini F, Mariotti S, Aloe S, et al. Soluble CD40 ligand (sCD40L) plasma levels in lung cancer. Clin Cancer Res. 2004;10(2):610-4.
5. Ferroni P, Martini F, Portarena I, Massimiani G, Riondino S, La Farina F, et al. Novel High-Sensitive D-dimer determination predicts chemotherapy-associated venous thromboembolism in lung cancer patients. Clin Lung Cancer. 2012;13(6):482-7.
6. Ferroni P, Riondino S, Portarena I, Formica V, La Farina F, Martini F, et al. Association between increased tumor necrosis factor-alpha levels and acquired activated protein C resistance in patients with metastatic colorectal cancer. Int J Colorectal Dis. 2012;27(12):1561-7.
7. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and Predictors of Venous Thromboembolism (VTE) Among Ambulatory High-Risk Cancer Patients Undergoing Chemotherapy in the United States. Cancer. 2013;119(3):648-55.
8. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166(4):458-64.
9. Roselli M, Ferroni P, Riondino S, Mariotti S, Laudisi A, Vergati M, et al. Impact of chemotherapy on activated protein C-dependent thrombin generation - Association with VTE occurrence. Int J Cancer. 2013;133(5):1253-8.
10. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. J Am Med Ass. 2005;293(6):715-22.
11. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. Thromb Res. 2006;118(5):555-68.
12. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med. 2012;7(3):291-2.
13. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902-7.