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Prevalence and patterns of symptomatic thromboembolism in oncohematology

DINO SGARABOTTO, PAOLO PRANDONI, PIERO MARIA STEFANI, FABIO SCANO, FABRIZIO VIANELLO, ROBERTO SARTORI, FRANCESCO PIETROGRANDE, ANDREA CAENAZZO, ANTONIO GIROLAMI
Second Chair of Internal Medicine, Institute of Medical Semeiotics, University Hospital of Padua, Italy

ABSTRACT

Background and Objective. **Approximately 15% of patients with cancer will experience a thrombotic episode at some time. Some patients are at particularly high risk depending on the histology of the malignant disease. The aim of the study was to determine the actual prevalence of thrombotic episodes in oncohematologic patients.**

Design and Methods. **We conducted a retrospective cohort analysis on a total of 515 patients that were admitted to the out-patients clinic (Institute of Medical Semeiotics) from January 1, 1986 to January 31, 1996. Two main groups were selected for this study: 133 patients suffering from a myeloproliferative disorder and 382 patients affected by a lymphoproliferative disorder. Follow-up lasted a median of 33 months in both groups (range 3-144 months). The difference between the observed events for each group was estimated by the odds ratio and chi square. Age and sex distribution were estimated by the Mann-Whitney test. Distribution of overall survival was estimated by the Kaplan-Meier method and compared between groups (DVT patients and non DVT patients) by the log-rank test.**

Results. **Twenty-three patients experienced a venous thrombotic disorder. The prevalence of deep vein thrombosis (DVT) in myeloproliferative and lymphoproliferative disorders was 8.27% (n=11) and 3.14% (n=12) respectively (odds ratio = 0,36; 95% CI= 0,14-0,90; chi-square= 4,94 p = 0,028). DVT was apparently idiopathic in 17 cases. In 4 patients another cancer was present; in the remaining 2 patients the thrombotic episode was associated with other predisposing factors. Although 7 of the 23 patients with DVT died, we cannot find any difference in the overall survival compared to oncohematologic patients who did not experience DVT.**

Interpretation and Conclusions. **The prevalence of symptomatic DVT in the oncohematological patients is lower than reported for solid tumor. Patients affected by myeloproliferative disease have a higher risk of developing thrombosis. DVT if well-treated does not influence the survival of oncohematological patients.**

Key words: deep vein thrombosis, thromboembolism, cancer, hematological neoplasms

Correspondence: Fabrizio Vianello, Institute of Medical Semeiotics, Second Chair of Medicine, Padua University, via Ospedale 105, Padua, Italy.
Phone: international +39-49-8212650 • Fax: international +39-49-657391 • E-mail: faviane@tin.it

Cancer patients are predisposed to hemostatic disorders. Approximately 15% of patients with cancer will have a thrombotic event at some time,[1] but some patients are at particularly high risk depending on the histology of the malignant disease involved.[2] In fact, mucin-secreting adenocarcinomas are commonly associated with thrombotic episodes whereas in certain neoplasms of the skin and brain the frequency is low. Recently, emphasis has been given to the potential threat of cancer therapy (both surgery and certain chemotherapy regimens) in increasing the risk for thromboembolic disease.[3] The pathogenesis of thrombosis in cancer is complex but three categories (often overlapping) can be distinguished:

i) release of tissue-factor-like material from tumor cells may be able to activate directly the clotting cascade and initiate a thrombotic event;[4]
ii) prolonged immobilization and venous compression caused by tumor mass;
iii) direct invasion of vascular structures by tumor may lead to thrombosis.[5]

The purpose of the present study is to establish the prevalence of DVT in oncohematological patients, to identify risk factors leading to a thrombotic event and to establish whether the thrombotic episode has an influence on patients' survival.

Materials and Methods

This is a retrospective cohort analysis conducted on a series of 515 consecutive patients referred to the outpatients clinic (Institute of Medical Semeiotics) from January 1, 1986 to January 31, 1996. Follow-up lasted a median of 33 months (range 3-119 months) and patients were classified according to the following oncohematological diseases: 65 low-grade non-Hodgkin lymphoma (LG-NHL), 79 high-grade non-Hodgkin lymphoma (HG-NHL), 56 multiple myeloma (MM), 60 chronic lymphocytic leukemia (CLL), 63 Hodgkin lymphoma (HD), 19 monoclonal gammopathy of unknown significance (MGUS), 21 hairy cell leukemia (HCL), 15 acute lymphoblastic leukemia (ALL), 4 cryoglobulinemia (CRIO), 15 idiopathic myelofibrosis (IMF), 26 chronic granulocytic leukemia (CGL), 10 polycythemia vera (PV), 46 myelodysplastic syndrome (MDS), 6 essential thrombocythemia (ET), 30 acute non lymphoblastic leukemia (ANLL).

The thrombotic episodes were classified in three main categories: a) apparently idiopathic DVT (no etiopathogenic criteria for DVT satisfied); b) DVT associated with other malignant disease (adenocarcinomas); c) DVT associated with other predisposing factors (prolonged immobilization, treatment with estroprogestinic). Some of the most frequent congenital (factor V Leiden, ATIII , protein C and S deficiency) and acquired (antiphospholipid antibodies) factors have been ruled out as the cause of DVT. All patients were interviewed to verify whether venous thromboembolism had occurred since the detection of the hematological disease. The following criteria were adopted to adjudicate a DVT of the lower or upper extremity:

i) the objective documentation of the disease, provided by invasive (phlebography) or non-invasive methods (compression ultrasonography, Doppler ultrasonography, impedance plethysmography);[6]
ii) a strong clinical history (admission to hospital and treatment with full-dose anticoagulant drugs for at least three months);[7,8]
iii) an equivocal clinical history associated with the positivity of instrumental criteria strongly suggestive of a previous DVT.[9]

For the diagnosis of PE, high probability V/Q scans and/or intraluminal fillings defects revealed by pulmonary angiography were accepted. Thrombosis in unusual sites was adjudicated by means of the appropriate tests (CT scan).

Age and sex distribution for the myeloproliferative and lymphoproliferative groups were estimated by the Mann-Whitney test. The difference between the observed events for each group was estimated by the odds ratio and chi-square test. Overall survival curves were obtained for both myeloproliferative and lymphoproliferative patients. The overall survival of DVT patients was compared to that of non-DVT patients. Overall survival was measured from the day of registration in the outpatient clinic until death from any cause; observation was censored for patients last known to be alive. Distribution of overall survival was estimated by the method of Kaplan-Meier and compared between groups (DVT patients and no DVT patients) by the log-rank test.

Results

The overall mean age of the 515 patients was 60 years (median 64, range 18-90). In the myeloproliferative (n=133, male=68, female=65) and lymphoproliferative (n=382, male=189, female=193) group we found a mean age of 64.3 years (median 67, range 18-90) and of 60 years (median 64, range 18-89), respectively. No significant difference for the age was found between male and female patients nor between patients who developed DVT, compared with patients who did not. Females who experienced a thrombotic episode were found to be older than females without DVT (p=0.028). Considering only the patients with DVT, the mean age was 64.9 years (median 67.18, range 41-84)) and 68.7 years (median 64.5, range 30-87) for patients affected by myeloproliferative (n=11) and the lymphoproliferative (n=12) diseases (p = not significant), respectively. Sex distribution was significantly dishomogeneous (p = 0.002) with a prevalence of males in the lymphoproliferative group and females in the myeloproliferative group, although we cannot find any difference for the age of patients in each group.

A venous thromboembolic disorder was recognized in twenty-three of 515 oncohematological patients. One or more episodes of DVT were observed in patients affected by HD, NHL, MM, CGL, PV, IMF, MDS, ANLL (Tables 1 and 2). No DVT episodes were observed in patients affected by CLL, HCL, ALL, MGUS, CRIO and ET. The prevalence of symptomatic DVT in myeloproliferative and lymphoproliferative disorders was 8.27% (n=11) and 3.14% (n=12), respectively (odds-ratio = 0.36; 95% CI= 0.14-0.90; chi-square= 4.94; p = 0.028). Among all the 23 patients with DVT, exposure to estrogen was found in two female patients affected by lymphoproliferative disease (one patient of childbearing age and one patient in estroprogestinic therapy) whereas all the other women were of post-menopausal age and had not received estrogenic substitutive therapy. DVT was apparently idiopathic in 17 cases whereas in 4 patients another cancer was present (1 colon adenocarcinoma, 2 prostate adenocarcinomas and 1 pancreas adenocarcinoma); in the remaining 2 patients the thrombotic episode was related to other predis-

Table 1. Oncohematologic patients who developed a DVT event.

HG	*LG*	*MM*	*HD*	*IMF*	*CGL*	*MDS*	*ANLL*	*PV*
n. of patients for each disease								
79	65	56	63	15	26	46	30	10
n. of patients with DVT								
6	2	2	2	3	3	3	1	1
DVT prevalence								
7.5%	3%	3.57%	3.17%	20%	11.53%	6.52%	3.33%	10%
mean age								
60.6	72	78	50	62.6	57.6	66.3	64	60
range								
29-70	70-74	73-83	29-71	47-81	44-65	59-75	–	–

LG (low-grade non Hodgkin lymphoma), HG (high-grade non Hodgkin lymphoma), MM (multiple myeloma), HD (Hodgkin's disease), IMF (idiopathic myelofibrosis), CGL (chronic granulocytic leukemia), MDS (myelodysplastic syndrome), ANLL (acute non lymphoblastic leukemia), PV (polycythemia vera).

Table 2. DVT episodes observed in myeloproliferative and lymphoproliferative patient.

Patients	*Sex*	*Age*	*Disease*	*Site of the DVT event*	*Presence of bulky tumour growth*	*Presence of other cancer*	*Predisposing factor*
BT†	M	47	IMF	LL[3]		–	–
BA	M	68	CGL	LL		–	–
BL	F	69	HG-NHL	LL	Retroperitoneal	–	–
BG	F	81	IMF	LL+intra-abdominal + PE[2]		–	–
BL	M	70	LG-NHL	LL		–	–
CG	M	60	PV	Intra-abdominal		–	–
DE	F	75	MDS	LL+PE[2]		–	–
CA†	F	62	HG-NHL	LL+Intra-abdominal	Intra-abdominal	–	–
FM†	F	29	HG-NHL	UL[3]	Mediastinal	–	–
LG	M	64	ANLL	LL		–	–
MA	F	83	MM	LL		–	–
TL†	F	70	HG-NHL	UL	Axillary	–	–
VS†	M	44	CGL	UL		–	–
ZE†	M	69	HG-NHL	Retinic vein		–	–
AE	F	71	HD	PE		–	–
PF	F	74	LG-NHL	LL		–	–
DC†	F	65	HG-NHL	LL	Intra-abdominal	–	–
BN	M	65	MDS	LL		Colon ad.[4]	–
BO	M	65	CGL	LL		Prostate ad.	–
GG	M	60	IMF	Intra-abdominal		Prostate ad.	–
CM†	F	59	MDS	PE[2]		Pancreas ad.	–
CL	F	29	HD	Intra-cranial sinus		–	Estroprogestinic therapy
FO	F	73	MM	LL		–	Immobilization

[1]Age of the patients is referred to the moment in which the oncohematological disease has been diagnosed; [2]PE: pulmonary embolism; [3]LL: lower limb, UL: upper limb; [4]ad.: adenocarcinomas.

posing factors (1 HD patient on estroprogestinic therapy, 1 MM obese patient subjected to a prolonged immobilization). The prevalence of a second neoplasia in the all the 515 oncohematological patients was 3.7% (n=19), 3% in the 492 patients who did not experience DVT (n=15) and 17% in the 23 patients with DVT (n=4), respectively. The lower limb was the most observed site of the thrombotic episode both in cases related to the oncohematological disease (11 cases: 6 patients of the lymphoproliferative group and 5 cases of the myeloproliferative group) and in those cases related to other predisposing factors (3 cases: 1 patient of the lymphoproliferative group and 2 cases belonging to the myeloproliferative group). Pulmonary embolism was detected in three patients with DVT secondary to the oncohematological disease, and in patient (1 case of MDS) with DVT associated with another malignant disease. DVT of the upper limb was documented only in those cases secondary to the oncohematological disease (3 cases: 2 patients of the lymphoproliferative group and 1 myeloproliferative patient). Intra-abdominal thrombosis was observed in 3 cases secondary to the oncohematological disease (2 patients of the myeloproliferative group and 1 lymphoproliferative patients) and in 1 myeloproliferative patient with an adenocarcinoma of prostate. We also observed other sites of DVT: one NHL patient developed a thrombotic episode of the retinic vein and one HD patient on a relapses-free survival since 18 months developed intracranial sinus thrombosis related to estroprogestinic (see Table 2).

Five HG-NHL patients with bulky disease who developed an episode of DVT during chemotherapy were on a high-dose steroid regimen with a large lymph node mass causing a compression of veins. Of the remaining three patients with NHL (1 HG and 2 LG cases) without *bulky disease* we were not able to identify any predisposing factor for DVT. Patients with DVT received scheduled chemotherapy regimens on completion of one week of anticoagulant therapy was completed. We did not document any intravenous chemotherapy-related thrombotic episode and all except one of the DVT cases of the upper limb (1 case of CGL) were induced by bulky tumour growth at the site of the thrombosis.

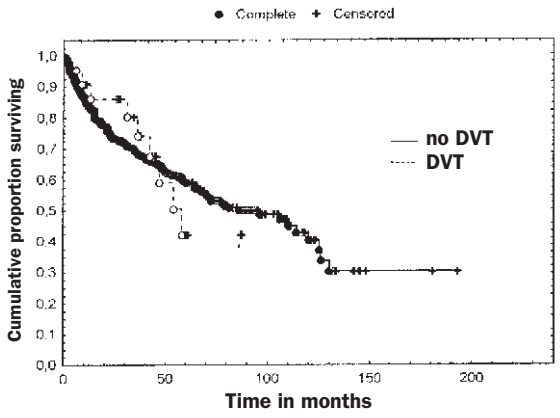

Figure 1. The overall survival of patients with lymphoproliferative and myeloproliferative disease who developed an episode of DVT did not differ from that of oncohematological patients who did not.

Although 7 of the 23 patients died, the overall survival of patients with lymphoproliferative and myeloproliferative disease that developed an episode of DVT did not differ from that of oncohematologic patients who did not (Figure 1).

A hemorrhagic complication developed in 6 out of 23 patients (16%) receiving anticoagulation for DVT. A minor bleeding (epistaxis or purpura) was observed in three patients whereas 3 cases experienced a major hemorrhagic episode (melena in 2 NHL and disseminated intravascular coagulation in 1 IMF).

Discussion

This retrospective trial shows that the prevalence of DVT in oncohematological patients (4.3%) is lower when compared to that observed in patients with other solid tumors (10-20%).[2] The duration of follow-up was sufficient to allow a valid estimate. The prevalence of DVT in the myeloproliferative and lymphoproliferative group was 8.27% and 3.14%, respectively. Since we only focused on symptomatic thromboembolism, we could not establish the true prevalence of thrombotic disorders. However, the clinical implication of an asymptomatic thromboembolic event in this context is unclear. The lower limb was the most frequently observed site of the thrombotic episode. On the contrary, although the data was not statistically significant, all the DVT of the upper limb except one (1 case of CGL) were induced by bulky tumour growth at the site of the thrombosis. We did not document any intravenous chemotherapy-related thrombotic episodes. This is in contrast with other reports.[2,10]

In our study, intra-abdominal thrombosis was not related to any particular disease. This finding is in contrast with the observation of Cortelazzo *et al.*[11] which emphasizes the role of PV and ET in the pathogenesis of the abdominal thrombosis. This difference might be explained by the low representation of PV and ET in our study, although in our study myeloproliferative diseases seem to disclose a significantly higher risk of DVT than the lymphoproliferative group.

It is worth noting that in the lymphoproliferative group, five out of six patients suffering from HG-NHL experienced the thrombotic episode due to vein compression, suggesting that the bulky tumor growth might play a role in the pathogenesis of thrombosis. Moreover, it must be taken into consideration that high-steroid dose regimens probably contribute to the pathogenesis of DVT.

Hemorrhagic complications in the oncohematological patients treated with heparin or coumarin (16%) were somehow more frequent compared to the non-cancer patients on an anticoagulation therapy (5-10%).[12] However, the three episodes of major bleeding were probably related to the extension of the disease (melena due to infiltration of gut wall in the 2 cases of NHL) or to disease activity (DIC in the case of IMF). Taken together, these results confirm the view that in the oncohematological patients, hemorrhagic episodes still represent the major hemostatic complication.

Recently, Ottinger *et al.*[2] reported their experience with HG-NHL patients who developed an episode of DVT. The occurrence of DVT was found to be associated with an unsatisfactory response of HG-NHL to treatment and with an often fatal treatment-related complication. On the contrary, in our study we found no correlation between the onset of DVT and the response to HG-NHL to treatment. The lack of reduction of the overall survival of our DVT patients could be explained by the early treatment received by our patients. In the group of oncohematological patients with DVT we found a high frequency of second neoplasia although the comparison with the group who did not developed thrombosis is made difficult due to the very low number.

In conclusion, the prevalence of DVT in the oncohematological patients is lower with respect to other solid tumors. Thrombotic manifestations are more frequent in myeloproliferative disorders.

Furthermore, our findings reveal that DVT, if well treated, does not influence the survival of oncohematological patients.

The implication of a low prevalence of DVT in the oncohematological disease is that the routine use of antithrombotic prophylaxis is probably unjustified.

Contributions and Acknowledgments

AG, DS and PP were responsible for the conception of the study, its design and direct sueprvision; PMF, FS and RS were responsile for data handling, statistical analysis and interpretation; FV contributed to the analysis and wrote the paper; AC and FP collaborated in the study design and were the main clinicians involved.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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