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Venous thromboembolism is a relevant and underestimated adverse event in cancer patients treated in phase I studies

M Mandalà*[,1], F Grosso[2], C Vitalini[3], I Corradino[3], R Sanfilippo[4], S Colombini[3], M Clerici[3], R Labianca[1], A De Pascale[3] and S Marsoni[3]

[1]Division of Medical Oncology, Department of Oncology and Hematology, Ospedali Riuniti, Largo Barozzi 1, Bergamo 24128, Italy; [2]Department of Oncology and Haematology, Ospedale Santi Antonio e Biagio, 15121 Alessandria, Italy; [3]SENDO Foundation, 20122 Milan, Italy; [4]Adult Sarcoma Medical Oncology Unit, Cancer Medicine Department, National Cancer Institute, 20133 Milan, Italy

BACKGROUND: To investigate, retrospectively, the role of tumour histotype and antiangiogenic drugs for venous thromboembolism (VTE) development in advanced cancer patients treated in phase I studies.

METHODS: Patients enrolled and treated in phase I studies conducted by SENDO (Southern Europe New Drugs Organisation) were considered.

RESULTS: Data of 1415 patients were included in the analysis: 526 (37.2%) patients were males, median age was 57.3 years (range: 13–85). Fifty-six (3.96%) patients developed a VTE. At multivariate analysis gynaecologic (hazard ratio (HR): 2.8, 95% confidence interval (CI): 1.29–6.23, $P = 0.009$) and gastrointestinal tumours (HR: 3.23, 95% CI: 1.18–8.87, $P = 0.023$) as well as combination regimens of cytotoxic and antiangiogenic agents (HR: 2.6, 95% CI: 1.11–6.30, $P = 0.028$), white blood cell $> 11\,000\ \mu l^{-1}$ (HR: 2.59, 95% CI: 1.10–6.09, $P = 0.028$) and haemoglobin $< 10\ g\ dl^{-1}$ (HR: 3.1, 95% CI: 1.07–8.94, $P = 0.037$) were statistically correlated with VTE development. Venous thromboembolism was the fourth most common cause of drug discontinuation. The median time from first drug administration to discontinuation was 1.4 for VTE and 2.3 months for the other adverse events ($P = 0.02$).

CONCLUSION: Venous thromboembolism is a relatively common complication among patients treated in the context of phase I studies, and may lead to early drug discontinuation. A greater risk of developing VTE is associated with the diagnosis of gynaecologic and gastrointestinal tumours and the combined use of chemotherapy and antiangiogenic drugs.

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Phase I studies are designed primarily to identify the maximum tolerated dose (MTD) for further clinical development of new drugs, and to evaluate their tolerability and toxicity profile. They include first-in-human studies as well as studies that combine two or more experimental or previously approved drugs for the first time (Maur and Sessa, 2007).

The clinical benefits of Phase I trials are limited, whereas toxicity-related risks in patients entering these studies may be considerable. Additionally, patients who are considered for these studies are usually in a vulnerable position, having advanced malignancies with no standard therapeutic options.

The assessment of dose-limiting toxicities (DLTs) is critical in phase I cancer clinical trials, as this represents the primary end point to determine the MTD, and an accurate reporting of safety data is crucial in the early phase of drug development.

In cancer patients, venous thromboembolism (VTE) is a relevant cause of morbidity and mortality negatively impacting on quality of life and health-care costs (Kahn *et al*, 2005). Cancer is a well-recognised independent risk factor for VTE, with almost one-fifth of all new VTE events associated with active cancer. Cancer patients have a 4- to 7-fold higher risk for VTE than patients without cancer, and about 10% of them will suffer a VTE episode during their life time, mostly while on chemotherapy (Falanga and Zacharski, 2005).

Despite the general perception that the incidence of VTE complications in metastatic patients is a high, few data are available for patients participating in phase I studies, in particular concerning the possible influence of tumour histotype and type of treatment (Vemulapalli *et al*, 2009; Mandala *et al*, 2012). Furthermore, there is no information regarding the relevance and the timing of VTE in the context of the commonly reported toxicities.

In a recent review evaluating how DLTs have been defined in oncology phase I trials of molecular target agents, VTE was never found to be part of any DLT definition (Le Tourneau *et al*, 2011).

The ideal setting to investigate this issue is a prospective database in which clinical data have been prospectively collected during the studies, including VTE.

In a previous paper, we validated the Khorana's score in patients treated in phase I studies (Mandala *et al*, 2010). In the present paper, we investigate the role of tumour histotype and chemotherapy with antiangiogenic drugs for the VTE development. Furthermore, we evaluate the relevance of VTE in the context of the commonly reported haematologic and non-haematologic toxicities.

*Correspondence: Dr M Mandalà; E-mail: mariomandala@tin.it
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PATIENTS AND METHODS

The trials and patients database, consisting of 1415 patients enrolled between 2000 and 2010 in 15 centres participating in the Southern Europe New Drugs Organisation (SENDO) Foundation phase I trials, have been previously described in detail (Mandala *et al*, 2012). In the current study, we considered all adverse events (AEs) occurring from the first dose of the study treatment up to 30 days after treatment discontinuation. All AEs were reviewed by the SENDO Medical Officer.

The study population was classified according to demographic and cancer-related characteristics (age, gender, tumour type) and to the type of antitumour therapy received in the study (cytotoxic drugs and/or different types of target therapies).

To investigate a possible difference in the time to progression and objective response rate between patients with and without VTE, a random selection of patients not experiencing VTE was performed and represented the control group: for each patient with VTE, two patients without VTE were matched according to tumour type, age (± 5), gender and type of antineoplastic treatment (e.g., cytotoxic therapy, antiangiogenic/antivascular/other target therapy, combination of two different treatment modalities).

All the AEs, including VTE, were prospectively collected during the study protocols.

In all studies but one requiring prophylaxis with acetylsalicylic acid no primary antithrombotic prophylaxis was foreseen during treatment but anticoagulants at thromboprophylaxis dose were allowed at investigator's discretion.

The criterion to diagnose VTE by compression US was non-compressibility of a proximal vein. When symptoms suggestive for pulmonary embolism developed, a radionuclide lung scanning, a CT scan or both were performed.

Statistical methods

Descriptive statistics were applied to the study population to present demographic and clinical characteristics: median, mean, range for continuous variables; number and percentage for qualitative variables.

No stratification by study was applied because of the very limited sample sizes of most of these studies and of the low incidence of VTEs.

Univariate analyses were performed on variables identified as potential risk factors, that is, tumour and treatment type, white blood cells (WBC), platelet count and haemoglobin, by applying the log-rank test. All of these variables were incorporated in the multivariate proportional Cox model with sex and age, including platelet count, which was the only variable associated with a P-value of >0.05, but was nevertheless recognised as a known risk factor.

The results were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs).

The time to treatment discontinuation was defined as the time from anticancer treatment start to treatment withdrawal. The statistical difference between time to treatment discontinuation in patients discontinued due to VTE and patients discontinued due to other AEs was assessed by a log-rank test and the Kaplan–Meier plot was provided.

A comparison between patients experiencing VTE and patients not experiencing VTE was performed for time to progression and objective response rate. Time to progression in the two cohorts was calculated by applying the Kaplan–Meier analysis and the relevant survival curves were generated and compared with the results of the log-rank test. Finally, the χ^2 test was used to compare the proportion of patients responding to anticancer treatment in the two cohorts.

The analysis was performed using SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA, Version 9.2) software.

RESULTS

The study population consisted of 1415 patients treated with experimental antitumour agents.

Demographic and clinical characteristics of the patients are summarised in Table 1.

The median patients' age was 57.3 years (range: 13–85), 62.8% of patients were women, 90.7% were <70 years. The most common primary tumours were gynaecologic, sarcomas, gastrointestinal and lung cancers (Table 1). In patients with a diagnosis of metastatic disease, which represented $>80\%$ of the population ($N=1203$), over 60% of patients had previously received less than three chemotherapy regimens for advanced disease.

In the study population, the most common schemes included one or more cytotoxic agents only (49.9%) and a single anti-vascular drug (14.6%).

Among 1415 patients included in the analysis, 56 experienced a VTE event during the period from the first dose to 30 days after treatment discontinuation (maximum follow-up time), with an overall incidence of 3.96% and a median follow-up of 2 months (range: 0–26). The median time to VTE occurrence was 1.3 months (range: 0–11.3) with 25% and 75% of events occurring within 0.7 and 1.9 months, respectively.

The most common events were deep venous thrombosis accounting for 58.9% of all observed VTEs and pulmonary embolism (23.2%). Fourteen patients stopped treatment due to VTE and in two cases VTE (pulmonary embolism) resulted in death.

The VTE events were remarkably high in gynaecologic (6.2%) as well as in gastric and pancreatic cancer patients (9.6%) (Table 2). On the opposite patients with sarcoma had the lowest risk to develop VTE (2.2%). With respect to the type of treatment, VTE incidence was particularly high in patients treated with cytotoxic agents in combination with an antiangiogenic drug (8.9%) as compared with patients treated with other types of treatment, accounting for $\sim 4\%$ each ($P=0.0344$). Among gynaecologic and sarcoma patients treated with trabectedin (ET-743) as single agent the incidence of VTE was 8.5% and 0%, respectively ($P=0.01$).

At multivariate analysis, after adjusting for gender and age, gynaecologic (HR: 2.8, 95% CI: 1.29–6.23, $P=0.009$) and gastrointestinal tumours (HR 3.23, 95% CI: 1.18–8.87, $P=0.023$), cytotoxic plus antiangiogenic agents (HR: 2.6, 95% CI: 1.11–6.30, $P=0.028$), WBC $>11\,000\,\mu l^{-1}$ (HR: 2.6, 95% CI: 1.10–6.09, $P=0.029$)

Table 1 Patient's characteristics

	N	%
Age (N = 1415)		
<70 years	1284	90.7
⩾70 years	131	9.3
Gender (N = 1415)		
Female	889	62.8
Male	526	37.2
Tumour type (N = 1415)		
Gynaecologic	435	30.7
Lung	146	10.3
Pancreas/stomach	73	5.2
Sarcoma	182	12.9
Other tumour type	579	40.9
Treatment type (N = 1415)		
Only cytotoxic	706	49.9
Only target therapy	318	22.5
Cytotoxic and antiangiogenic	112	7.9
Cytotoxic and other target agent	279	19.7

Clinical Studies

Table 2 VTE events according to tumour histotype and treatment type

Covariates	Patients No	Patients with VTE	%	Median time to VTE (days)	*P*-value
Tumour type					
Gynaecologic	435	27	6.2	45	0.0028
Lung	146	5	3.4	7	
Pancreas/stomach	73	7	9.6	23	
Sarcoma	182	4	2.2	51	
Other tumour type	579	13	2.2	47	
Treatment type					
Only cytotoxic	706	22	3.1	48.5	0.0344
Only target therapy	318	12	3.8	16.5	
Cytotoxic and antiangiogenic	112	10	8.9	37.5	
Cytotoxic and other target agent	279	12	4.3	46.5	

Abbreviation: VTE = venous thromboembolism.

Table 3 Multivariate Cox Proportional Hazard Model of VTE events with age, sex, tumour histotype, treatment type, platelets, haemoglobin and WBC as covariate variables

Covariates	χ^2	*P*-value	Hazard ratio	95% HR
Sex				
Female	0.2742	0.6005	1.220	0.580–2.565
Male	—	—	1	—
Age (years)				
$\geqslant 70$	0.1358	0.7125	1.169	0.510–2.677
<70	—	—	1	—
Tumour histoype				
Gynaecologic	6.7467	0.0094	2.836	1.292–6.228
Lung	1.7066	0.1914	2.019	0.704–5.792
Pancreas/stomach	5.1764	0.0229	3.230	1.176–8.867
Sarcoma	0.0113	0.9154	1.064	0.340–3.329
Other tumour type	—	—	1	—
Treatment type				
Only target therapy	2.4353	0.1186	1.768	0.864–3.615
Cytotoxic and antiangiogenic	4.8096	0.0283	2.644	1.109–6.305
Cytotoxic and other target agent	0.0230	0.8796	0.944	0.447–1.995
Only cytotoxic	—	—	1	1
Platelets				
$\geqslant 350 \times 10E9\,L^{-1}$	0.0782	0.7798	0.910	0.469–1.764
$<350 \times 10E9\,L^{-1}$	—	—	1	1
Haemoglobin				
$<100\,g\,L^{-1}$	4.3686	0.0366	3.098	1.073–8.943
$\geqslant 100\,g\,L^{-1}$	—	—	1	1
WBC				
$>11 \times 10E9\,L^{-1}$	4.7733	0.0289	2.592	1.103–6.090
$\leqslant 11 \times 10E9\,L^{-1}$	—	—	1	1

Abbreviations: HR = hazard ratio; VTE = venous thromboembolism; WBC = white blood cells.

and haemoglobin $<10\,g\,dl^{-1}$ (HR: 3.1, 95% CI: 1.07–8.94, $P=0.037$) were statistically correlated with VTE development (Table 3).

The flow chart showing patient disposition until treatment discontinuation is reported in Figure 1. The most common reason for drug discontinuation was the progression of the disease (63.9% of patients), followed by AE (16.3%). Among this latter subgroup, in 6.1% of the cases VTE was the only reason for drug discontinuation.

The AEs causing most frequently drug discontinuation are shown in Figure 2.

Bone marrow toxicity was the most common reason (45.2%) followed by peripheral neurological toxicity (7.8%). Venous thromboembolism was the fourth most common AE requiring drug discontinuation (Figure 2).

The median time from the first drug administration to treatment discontinuation was statistically different for withdrawals due to VTE as compared with withdrawals due to other AEs: 1.4 and 2.3 months, respectively ($P=0.02$) (Figure 3).

The analysis of response rate comparing patients with and without VTE showed a response rate of 12.5% and 8.9%, respectively ($P=0.47$). Likewise, time to progression did not differ between the two cohorts (Figure 4). Response rate and time to progression cohorts were generated by matching each patient with VTE with two patients without VTE according to tumour type, age (± 5), gender and treatment type; perfect matching was achieved in 91 (81.3%) of the controls randomly selected, in the other cases, matching between patients with/without VTE was done according to three or two of the variables listed above.

DISCUSSION

Thrombosis is a leading complication in advanced cancer representing a major health burden for patients and care providers. Our data clearly demonstrate that 4% of cancer patients treated within the context of early phase anticancer experimental treatments, including target therapies, will develop a VTE episode and, as a consequence, stop treatment, negatively impacting on the results of the studies in which they were enrolled. In this study, we further refine the search for VTE predictors in this special patient's population to provide guidance for the prophylaxis of specific high-risk subgroups. The remarkably high incidence observed in gynaecologic and gastric/pancreatic cancer patients in our series matches well with a previous report (Vemulapalli *et al*, 2009), observing a VTE incidence of 11.8%. In our series, the role of tumour histotype is well supported by the difference in VTE rate observed in gynaecologic tumours and in sarcoma patients receiving the same antitumour drug, trabectidin. The VTE incidence in gynaecologic tumours patients was 8.5% and 0% in the sarcoma patients, respectively ($P=0.01$).

The combined use of an antiangiogenic plus a cytotoxic agent also identifies a group of subjects with a high risk of developing VTE (8.9% *vs* 3.5% of patients treated with other regimens). Again this increased risk is consistent with the results reported in phase III studies combining a cytotoxic with an antiangiogenic (Kabbinavar *et al*, 2009) as well as in previous meta-analyses (Nalluri *et al*, 2008; Cao *et al*, 2009). There are no hints that the higher incidence observed in this subgroup could be explained by a longer time on study implying a higher probability to observe a VTE, since the median observation period of this group (2.2 months) does not show any significant difference as compared with that of the other antitumour regimens (2.0 months) and considering also that 75% of the observed VTEs occurred within 1.9 months after treatment start.

In our study, we also found an association of leukocytosis with VTE. Several reasons may justify these findings: it is well known that there is a cross-talk between granulocytes and platelets and/or endothelial cells; furthermore, in cancer patients, leukocytosis may also be a surrogate for advanced disease burden not captured by stage classification.

In our series, VTE was the fourth most common AE as cause of drug discontinuation (6.1%), being bone marrow toxicity the most frequent reason for treatment withdrawal (45.2%) followed by peripheral neurological toxicity (7.8%), infection and liver function abnormalities (7% each). Of notice the observation that VTE was more frequent than neuropathic pain, nausea/vomiting, diarrhoea, renal function abnormalities, hand foot syndrome and

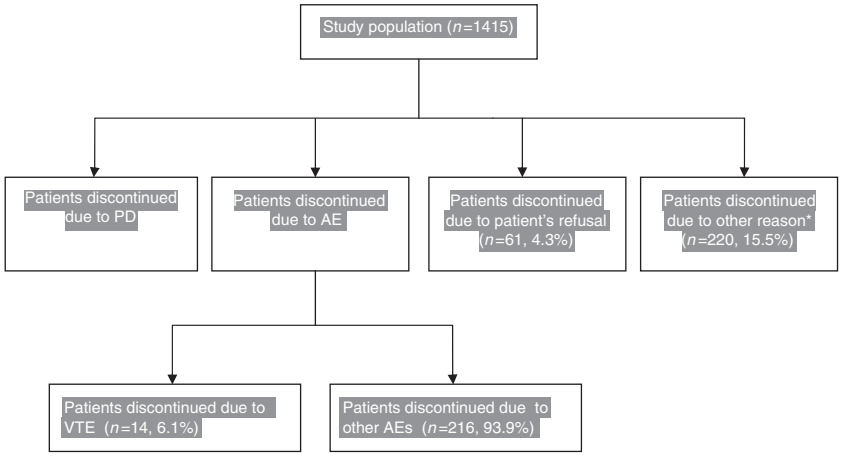

Figure 1 Flow chart of patient disposition until treatment discontinuation.

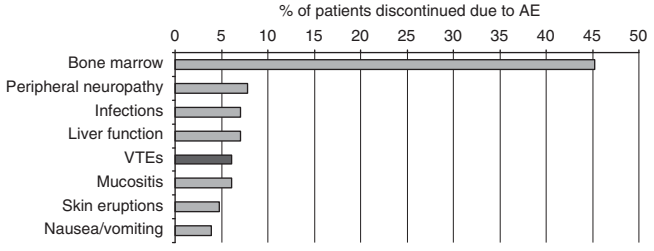

Figure 2 Adverse event as cause of treatment discontinuation.

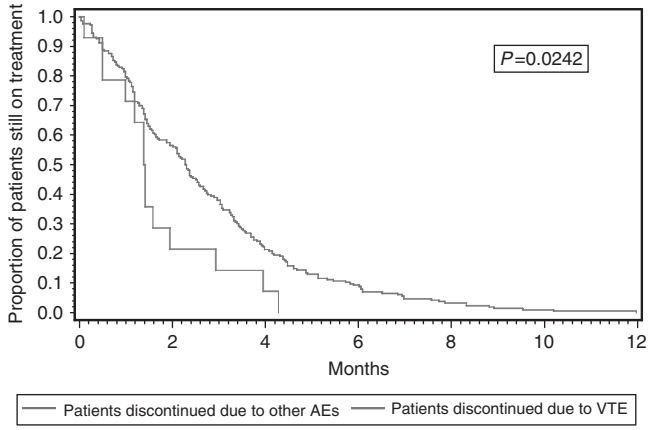

Figure 3 Kaplan–Meier curve of time to treatment discontinuation (only for patients discontinued due to AEs). *P*-value for the log-rank test is shown.

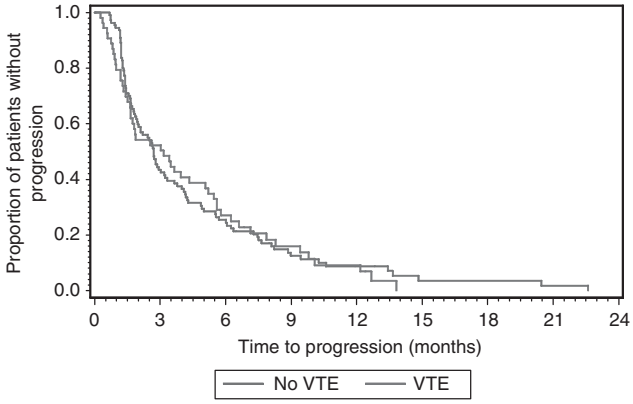

Figure 4 Kaplan–Meier curve of time to disease progression.

other skin toxicities, generally perceived by the oncologists as toxicities particularly worthy of attention.

In a recent review evaluating how DLTs have been defined in oncology phase I trials of molecular target agents, VTE was never found to be part of any DLT definition (Le Tourneau *et al*, 2011). Likewise, VTE is not reported as toxicity in most of the trials evaluating cytotoxic drugs. In a recent European Drug Development Network (EDDN) collaboration study (14), including high quality data from 2232 patients treated in the context of phase I studies in 14 major European institutions between 2005 and 2007, VTE was not reported in most of the considered trials.

All the above data set well the scene regarding the underestimation of these events in the context of new drug development and raise the issue of a more adequate collection of toxicity data in order to well describe one of the most important causes of morbidity in cancer patients.

We are not able to comment on awareness *per se* and neither on attitude to VTE, since these would need qualitative methodologies to investigate. Further studies are needed to clarify this issue within the oncology community.

The strength of this study is its relative large cohort of patients, all treated in SENDO centres, with prospective safety data collection; on the other hand, a limitation is that by selecting only symptomatic, objectively diagnosed VTEs, a number of asymptomatic VTEs may have been missed with a possible consequent underestimation of the risk of this type of event. Furthermore, we did not investigate the role of the D-dimer and available thrombin generation. A prospective randomised study was carried out in 32 metastatic breast cancer patients receiving chemotherapy (Falanga *et al*, 1998). In this study, the D-dimer was elevated in cancer patients as compared with normal controls and declined in 16 patients receiving warfarin prophylaxis. Nevertheless, none of the laboratory variables could predict thrombosis in individual patients. Furthermore, it should be taken into consideration that in the above-mentioned EDDN trial (Cassier *et al*, 2011) in 2 years >2000 patients entered phase I trials: these figures demonstrate that patients entering phase I studies are not a niche among cancer patients.

Although in this study 137 patients (9.7%) received at least one thromboprophylactic dose of low molecular weight heparin, in absence of VTE, it was not possible to evaluate the impact of anticoagulant thromboprophylaxis mainly because of the heterogeneity with regards to the beginning and the duration of thromboprophylaxis.

The median time from the first drug administration to treatment discontinuation was statistically different for patients withdrawn due to VTE as compared with patients withdrawn due to other AEs: 1.4 and 2.3 months, respectively ($P = 0.02$) (Figure 3), thus most of these events occur while patients are on treatment and lead to earlier treatment discontinuation. The clinical implication of these findings is that VTE may represent a cause of premature withdrawal of a potentially active drug in cancer patients.

In summary our data demonstrate that, within the context of early clinical trials of new anticancer drugs, VTE is far from being a negligible toxicity and represents the fourth and earliest cause of treatment discontinuation. While no causative explanations can be derived from a purely clinical database such ours, the strength of the relationship between VTE occurrence and specific tumours types, treatments combinations and tumour burden-related conditions suggest that these patients have a much higher chance of developing VTE than other patients. Since their risk is comparable to that observed in other high-risk settings such as that of the hospitalised, medically ill patients for whom prophylaxis is recommended by international guidelines (Lyman *et al*, 2007; Mandala *et al*, 2010), should these results be confirmed in other series, primary thromboprophylaxis should be given to them as well. Finally, our results pose the question of VTE underestimation in the current literature and in the planning of early clinical trials.

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