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Incidence and clinical implications of venous thromboembolism in advanced colorectal cancer patients: The 'GISCAD-alternating schedule' study findings

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ABSTRACT

Aim of the study: To investigate the incidence and clinical implications of venous thromboembolism (VTE) in advanced colorectal cancer (ACC) patients treated and followed-up through a prospective randomised trial, comparing FOLFIRI chemotherapy given as an intermittent or as a continuous schedule.

Patients, materials and methods: A total of 266 patients were randomised by 15 experimental centres: 168 (63.2%) were males, median age: 64.6 years, age range: 37–76 years. Almost all (95.5%) patients had metastatic disease, while the remainder were classified with locally advanced irresectable disease. For 138 (51.9%) of the patients, the chemotherapy treatment was intermittent FOLFIRI and the remaining patients received continuous treatment. All toxicities, including VTE, were prospectively collected.

Results: During the study protocol, the central data management gathered two cases of VTE. Our analysis retrieved 27 (10.2%) patients who developed a VTE, almost all (89%) during the course of chemotherapy treatment: 20 out of 27 during FOLFIRI, the remaining 7 during following lines or follow-up. VTE was the most frequent grade 3/4 toxicity. The incidence of VTE was significantly increased in the patients receiving continuous rather than intermittent treatment (HR 2.67, 95% CI 1.17–6.10; $p < 0.02$).

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Conclusion: VTE is a common complication among advanced colorectal cancer patients and yet this type of toxicity is widely underestimated. In this randomised trial, VTE was the most frequent grade 3/4 toxicity. Use of an intermittent schedule is associated with a reduced risk of developing VTE.

1. Introduction

The close link between cancer and venous thromboembolism (VTE) has been under evaluation since Trousseau's time. Although VTE is a common complication in cancer patients, there is a general perception that this type of complication is underestimated.[1]

The relationship between cancer, chemotherapy and thrombosis has been more extensively investigated in breast cancer patients. Despite the general perception that there is a high incidence of thromboembolic complications in patients with mucinous carcinoma of the pancreas and gastrointestinal (GI) tract, few data are available for colorectal cancer (CC) patients receiving chemotherapy. A recent retrospective study on patients with various solid tumours found a remarkably high incidence (7%) of VTE in a group of 39 colon cancer patients during chemotherapy.[2] Few clinical trials have investigated what contribution anticancer drugs and cancer make to thrombogenesis.

Ideally, in advanced CC, the best setting for investigating the role of these two thrombogenic factors is a prospective randomised trial comparing the same chemotherapy schedule with different administration timing. The rates of thrombosis in advanced CC patients should be compared during periods with and without chemotherapy.

Recently, we performed a prospective trial to assess whether intermittent FOLFIRI – l-leucovorin (LLV) 100/mg/m^2 iv + 5FU 400 mg/m^2 iv bolus + 5FU 600 mg/m^2 22 h continuous infusion, day 1 and 2 + CPT-11 180 mg/m^2 day 1 administered every 2 weeks, 2 months on and 2 months off – is at least as effective as the same regimen given continuously; both were administered until the patients with advanced CC and not previously exposed to chemotherapy for advanced disease showed signs of progression or unacceptable toxicity.[3] Since most of VTE events occur within the first 4 months of chemotherapy[4], the original design of our trial allowed us to investigate the incidence of VTE in the intermittent schedule versus the classical schedule in advanced CC out-patients. In addition, we reviewed the relevant literature with special emphasis on the reported VTE incidence in recent (2004–2007) prospective randomised clinical trials by investigating the role of chemotherapy in locally advanced or metastatic CC patients.

2. Patients and study design

The study was conducted on patients enrolled in a subgroup of the centres that participated in the previously described study.[3]

The criteria for inclusion were: (i) histological diagnosis of advanced CC, not amenable to surgical resection or ablation (e.g. with radiofrequency) of metastases, (ii) an ECOG-PS < 2 and (iii) normal renal, hepatic and bone marrow functions. The criteria for exclusion included (i) serious concomitant diseases not adequately responding to specific therapy, (ii) second cancer diagnosed </= than 5 years from CC occurrence, (iii) brain metastases; (iv) pregnancy, (v) more than 4 weeks between disease staging and onset of treatment, (vi) previous radiotherapy on the measurable sites and (vii) previous chemotherapy for the advanced disease. The study protocol was approved by the Local Ethics Committees and all patients gave their informed consent.

All the toxicities, including VTE, were prospectively collected during the study protocol.

Information on age, gender, histopathology, surgical and medical treatment was retrieved for each patient, as well as on overall tumour response, progression free survival (PFS) and overall survival (OS). Patients were treated in the ambulatory setting; the patients did not receive a primary prophylaxis during treatment.

The medical charts and the radiological history of all the patients were checked as regards to (i) ultrasonography (US) of the extremities, (ii) computed tomography (CT) of the chest and abdomen and (iii) perfusion/ventilation lung scan. We actively searched the records and radiological reports of all the patients with proven VTE for indicators of tumour load at the time of the event. The criterion used to diagnose VTE by compression US was non-compressibility of a proximal vein. When symptoms developed suggesting pulmonary embolism (PE), a radionuclide lung scan or a CT scan or both were performed.

2.1. *Statistical methods*

All patients meeting the criteria for eligibility were considered for analysis according to the line of treatment currently being received.

PFS was defined as the time from the onset of chemotherapy to the first appearance of progressive disease or death for any cause; patients known to be alive and free of progressive disease at the time of analysis were censored at their last available follow-up assessment.

OS was defined as the time from the beginning of chemotherapy to the date of death from any cause or the date of the last follow-up.

Thrombosis free interval (TFI) was defined as the time from the beginning of chemotherapy to the date of VTE occurrence.

VTE was included both irrespective of the time of occurrence and by distinguishing between occurrence during or after chemotherapy.

Survival curves were estimated using the Kaplan–Meier method. The Cox proportional hazards model was used for univariate and multivariate analyses that test demographic

characteristics and clinical features for their association with PFS and OS. The results, expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs), are reported for each factor.

With this series in which approximately 260 patients progressed or died, the study showed a 90% capacity for detecting HRs of at least 2.0 associated with the group with VTE [expected to have a prevalence of about 10%] with a type I error of 5% for the bilateral test.

Statistical significance was set at $p < 0.05$. Analysis was performed using SAS (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA, Version 9.0) software.

3. Results

A total of 266 patients were randomised by 15 experimental centres.

Demographic and clinical characteristics of the patients are summarised in Table 1. One-hundred and sixty eight (63.2%) were males, median age: 64.6 years, age range: 37–76 years. Almost all (95.5%) patients had metastatic disease, while the remainder were classified with locally advanced irresectable disease.

Chemotherapy treatment was intermittent FOLFIRI for 138 (51.9%) patients, while the remainder received continuous treatment. Twenty seven (10.2%) patients developed a VTE, almost all (89%) during chemotherapy treatment: 20 out of 27 during FOLFIRI, further 7 during following lines or follow-up. We retrieved four PE events, three of which occurred during the first line of chemotherapy. All these patients stopped treatment due to VTE toxicity. Ten patients developed a catheter-related thrombosis. Finally, for three patients, a lower vena cava thrombosis was recorded during the restaging of the disease. The remaining patients developed a lower limb VTE. Two patients, with VTE during the first cycle of chemotherapy, developed a recurrence during the following lines of treatment. We did not retrieve any fatal events; 23 patients were successfully treated with a low molecular weight heparin, while patients with PE were hospitalised and received anticoagulation with unfractioned heparin followed by low molecular weight heparin at home. G3–4 toxicities are reported in Table 3.

Table 1 – Demographic and clinical characteristics of patients

	VTE		Total
	No (239)	Yes (27)	
Age median (min–max)	64.7 (37–76)	63.9 (51–75)	64.6 (37–76)
Sex			
Male	149 (62.34)	19 (70.37)	168
Female	90 (37.66)	8 (29.63)	98
Site of tumour			
Colon	165 (69.33)	23 (85.19)	188
Rectum	73 (30.67)	4 (14.81)	77
Missing	1		1
Number of metastases			
0	10 (4.18)	2 (7.41)	12
1	169 (70.71)	14 (51.85)	183
>1	60 (25.10)	11(40.74)	71

At a median follow-up of 51 months, 256 (96.2%) patients progressed and 224 (84.2%) had died. Overall 263 (98.9%) patients progressed or died. For the group as a whole, the median PFS and OS were 6 and 18 months, respectively.

At univariate analysis (Table 2) of the presence of more than one metastatic site (HR 2.5, 95% CI 1.13–5.55; $p = 0.023$),

Table 2 – Univariate and multivariate analysis for thrombosis free interval (TFI), overall survival (OS) and progression free survival (PFS)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Thrombosis free interval				
Continuous FOLFIRI treatment	2.67 (1.17–6.10)	0.020	2.31 (0.99–5.36)	0.052
Number metastatic sites	2.51 (1.13–5.55)	0.023	2.37 (1.07–5.25)	0.034
Age	1.00 (0.95–1.05)	0.989	Not done	
Site (rectum versus colon)	0.41 (0.14–1.19)	0.102	Not done	
Sex	0.72 (0.31–1.64)	0.430	Not done	
Overall survival				
Continuous FOLFIRI treatment	1.15 (0.89–1.50)	0.289	Not done	
Number metastatic sites	1.51 (1.12–2.02)	0.007	Not done	
Age	1.01 (0.99–1.02)	0.582	Not done	
Site (rectum versus colon)	0.85 (0.64–1.14)	0.286	Not done	
Sex	1.05 (0.80–1.38)	0.729	Not done	
Progression free survival				
Continuous FOLFIRI treatment	0.93 (0.73–1.19)	0.558	Not done	
Number metastatic sites	1.11 (0.84–1.46)	0.451	Not done	
Age	1.00 (0.98–1.01)	0.592	Not done	
Site (rectum versus colon)	1.01 (0.78–1.32)	0.918	Not done	
Sex	1.12 (0.87–1.44)	0.362	Not done	

Table 3 – Toxicity (grade 3–4)

	Continuous	Intermittent
	FOLFIRI treatment	
	n (%)	*n* (%)
Diarrhoea	11 (8.7)	5 (3.6)
Nausea	4 (3.1)	4 (2.9)
Vomiting	3(2.3)	2 (1.4)
Alopecia	2 (1.6)	2 (1.4)
Mucositis (grade 2)	11 (8.6)	8 (5.8)
Leucopaenia	4 (3.1)	2 (1.4)
Anaemia	2 (1.6)	0
Thrombocytopaenia	5 (3.9)	2 (1.4)
Astenia	11 (8.7)	11 (8.7)
Pulmonary embolism	2 (1.6)	2 (1.4)
Deep venous thrombosis	17 (13.3)	6 (4.3)

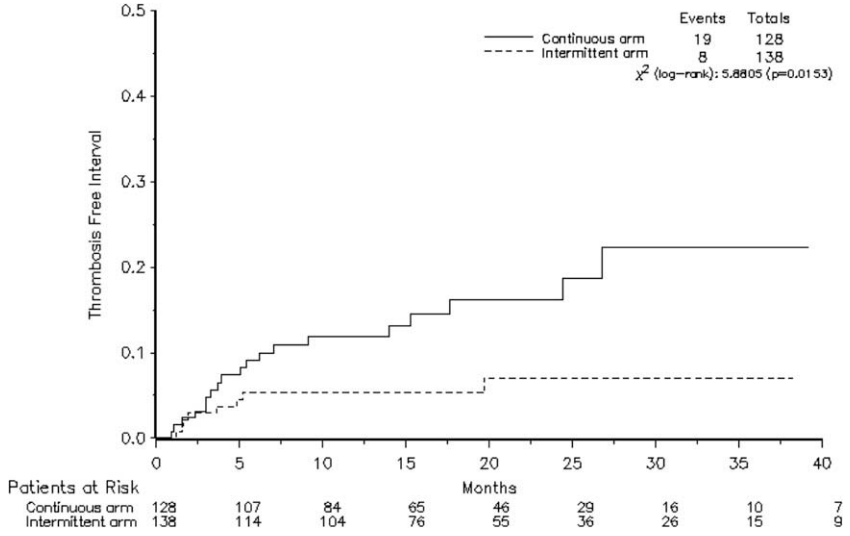

Fig. 1 – Thrombosis free interval in patients treated with continuous versus intermittent FOLFIRI (5FU, Irinotecan, folinic acid) schedule.

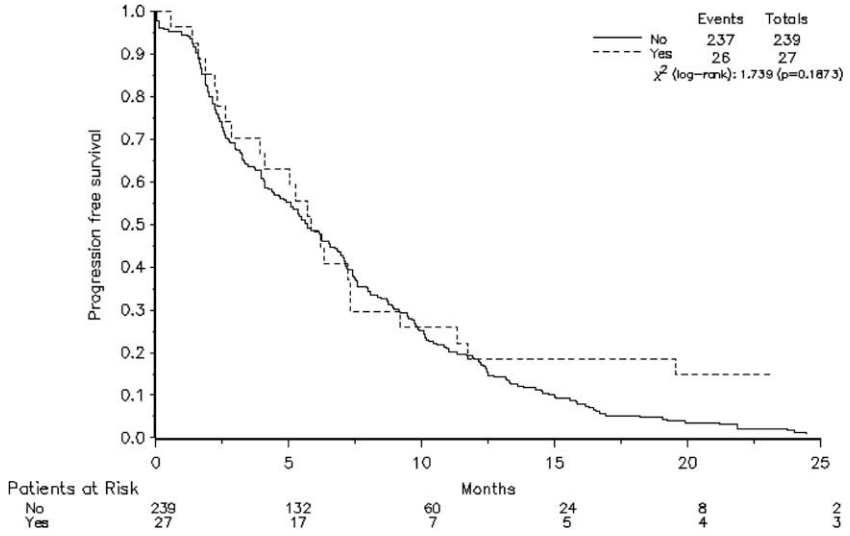

Fig. 2 – Progression free survival for patients with or without venous thromboembolism.

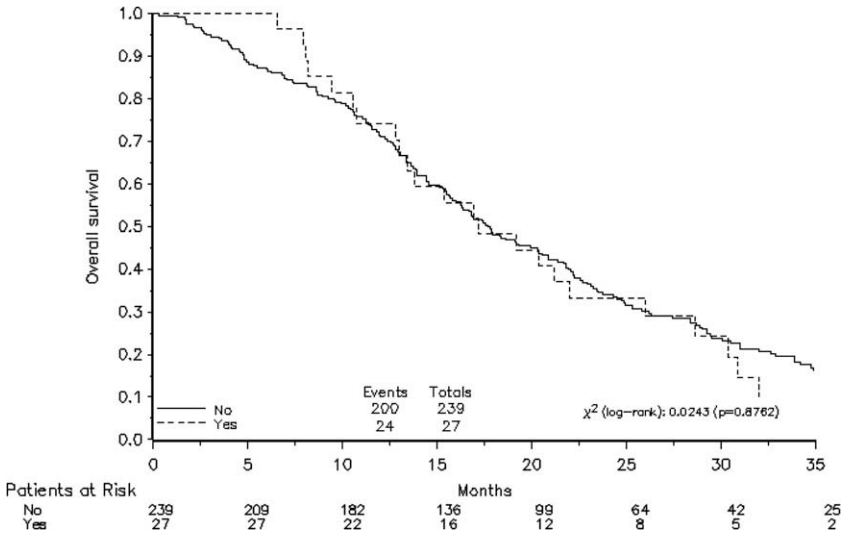

Fig. 3 – Overall survival for patients with or without venous thromboembolism.

continuous FOLFIRI treatment (HR 2.67, 95% CI 1.17–6.10; $p = 0.02$) was associated with a greater probability of a thrombosis occurrence. A multivariate assessment only confirmed a statistically significant association for the number of metastatic sites. Moreover, only the number of metastatic sites proved to be associated with a poorer OS, while PFS did not appear to be affected by any variables.

Fig. 1 shows the Kaplan–Meier curves for TFI according to FOLFIRI treatment, while PFS and OS are described in Figs. 2 and 3.

4. Review of the literature

We reviewed the literature with respect to thromboembolic events occurring in advanced colorectal cancer receiving a first line chemotherapy.

We ran an extensive Medline and Cancerlit review of the literature (2004–2007) to retrieve the reported VTE events in other randomised clinical trials, investigating first line chemotherapy in advanced CC patients. Various combinations of search terms were used depending on the requirements of the database being searched. These terms included: 'Thrombosis', 'Thromb*', 'Venous Thrombosis', 'Coagulation', 'Cancer', 'Tumor', 'Therapy', 'Chemotherapy', 'First Line', 'Randomised', 'Colon Cancer', 'Colorectal Cancer', 'Clinical', 'Study', 'Trial*'. We ruled out trials investigating chemotherapy in combination with 'targeted agents'. We gave priority to trials published in the last three years in order to analyse the safety of homogeneous treatments for advanced disease. In addition, updates regarding the toxicity analysis of previous published studies have been considered. It's worth noting that we reviewed the literature of studies that appeared in the major journals after publication of the US National Cancer Institute Criteria for common toxicity version 3, which clearly includes and grades VTE as non-haematological toxicity. We searched the 'Table of Toxicities' reported in the full-papers published in such important medical journals as: The Lancet, New England Journal of Medicine, Annals of Oncology, JAMA, Journal of the National Cancer Institute, Journal of Clinical Oncology, British Journal of Cancer, European Journal of Cancer and Cancer.

The literature research is reported in Table 4. Only 1 out of 28 (3.5%) randomised clinical trials reported this type of toxicity in the 'Table of Toxicities' and, overall, only 5/28 (17.8%) reported this type of toxicity in the text.[5–32]

Furthermore, it is remarkable that the most important clinical trial, assessing the efficacy and safety of irinotecan as first line chemotherapy, did not report any VTE occurrence.[33]

Finally, in 3 out of the 5 papers that did report VTE toxicity in the text, the incidence was less than 1%, which is clearly underestimated.

5. Discussion

The first important message from our study is that VTE is a very common toxicity in colorectal cancer patients receiving chemotherapy in an ambulatory setting. In our study, VTE was the most common grade 3/4 toxicity. To the best of our knowledge, this is the first study that evaluated clinical risk factors for VTE in the context of a prospective randomised trial. Otten et al. reported a 7% incidence of VTE in a small group of CC patients during chemotherapy with 5FU. However, this was a retrospective, not randomised study and the evaluable patients were only 39. Recently, Khorana et al. found that certain sites of cancer such as brain, pancreas, ovary, kidney, stomach and lung are associated with the highest rates of VTE.[34] In a prospective observational study of ambulatory cancer patients on chemotherapy, upper gastrointestinal cancers, lung cancer and lymphoma were independent predictors of VTE.[34] Our study extends these findings, suggesting that the incidence of VTE in CC patients is relevant. The rate of VTE is not only high, but the incidence reported in our study compares well with that reported in high risk hospitalised patients at risk to develop VTE, who

Table 4 – Incidence of venous thromboembolism in advanced colorectal cancer patients (2004–2007): an underestimated problem*

Author	Colorectal cancer patients (N)	Type of study*	Type of treatment	Incidence of VTE (%)
Feliu et al.[5]	94	Phase II randomised	Ralt.-Iri vs. Ralt.-ox.	Not reported
Van Cutsem et al.[6]	164	Phase II randomised	Iri. different doses	Not reported
Van Cutsem et al.[7]	1207	Phase III randomised	Capecitabine vs. 5FU/LV	Not reported
Bajetta et al.[8]	143	Phase II randomised	Uracil/Ftorafur/LV plus iri or ox.	Not reported
Souglakos et al.[9]	283	Phase III randomised	FOLFOXIRI vs. FOLFIRI	Not reported
Martoni et al.[10]	118	Phase II randomised	Xelox vs pvifox	0.8%
Garufi et al.[11]	68	Phase II randomised	Ir. plus 5Fucr. vs. Ir. cr.	Not reported
Noguè et al.[12]	237	Phase III randomised	Uracil/Ftorafur/LV vs. 5FU/LV	Not reported
Hospers et al.[13]	302	Phase III randomised	5FU bolus + Ox. vs. 5FU c.i. + Ox.	Not reported
Goldberg et al.[14]	305	Phase III randomised	IFL vs. FOLFOX	Not reported
Colucci et al.[15]	360	Phase III randomised	FOLFIRI vs. FOLFOX	Not reported
Tournigand et al.[16]	220	Phase III randomised	FOLFIRI vs. FOLFOX	0.8%
Kohne et al.[17]	430	Phase III randomised	AIO vs. AIO + Iri	Not reported
Fuchs et al.[18]	430	Phase III randomised	FOLFIRI vs. CapeIri vs. IFL	Not reported
Falcone et al.[19]	244	Phase III randomised	FOLFOXIRI vs. FOLFIRI	Not reported
Goldberg et al.[20]	795	Phase III randomised	IFL vs. FOLFOX vs. IROX	Not reported
Becouarn et al.[21]	80	Phase II randomised	IROX vs. FOLFIRI or FOLFOX	Not reported
Comella et al.[22]	274	Phase III randomised	OXAFAFU vs. IRIFAFU	Not reported
Kalofonos et al.[23]	295	Phase II randomised	OXAFAFU vs. IRIFAFU	Not reported
Delaunoit et al.[24]	108	Phase III randomised	OXAFAFU vs. IRIFAFU	Not reported
Koopman et al.[25]	820	Phase III randomised	Sequential vs. Combination (CAIRO)	10%
Seymour et al.[26]	2135	Phase III randomised	Sequential vs. Combination (MRC FOCUS)	Not Reported
Schoemaker et al.[27]	174	Phase II randomised	Iri. different schedules	Not reported
Porschen et al.[28]	474	Phase III randomised	CAPOX vs. FUFOX	Not Reported
Giacchetti et al.[29]	564	Phase III randomised	ChronoFLO4 FOLFOX2	Not reported
Ashley et al.[30]	383	Phase III randomised	IROX	Not reported
Diaz-Rubio et al.[31]	348	Phase III randomised	CAPOX vs. FUOX	4%
Tournigand et al.[32]	620	Phase III randomised	FOLFOX4 FOLFOX7	3.5%, 0.6%

Ralt., Raltitrexed; Iri, Irinotecan; Ox, Oxaliplatin; 5FU, 5- Fluorouracil; LV, Leucovorin; FOLFOXIRI, 5-Fluorouracil + Oxaliplatin + Irinotecan + Leucovorin; FOLFIRI, 5-Fluorouracil bolus and continuous infusional + Irinotecan + Leucovorin; Xelox, capecitabine + oxaliplatin; Pvifox, 5-FU continuous infusion + oxaliplatin; 5-FU cr, 5-Fluorouracil chronomodulated; Iri cr, Irinotecan Chronomodulated; FOLFIRI, 5-Fluorouracil + Irinotecan + Leucovorin; IFL, 5-Fluorouracil + Irinotecan + Leucovorin; FOLFOX, 5-Fluorouracil bolus and continuous infusional + Oxaliplatin + Leucovorin; CapeIri, Capecitabine + Irinotecan; IROX, Irinotecan + Oxaliplatin; OXAFAFU, 5-Fluorouracil bolus + Oxaliplatin + Leucovorin; IRIFAFU, 5-Fluorouracil bolus + Irinotecan + Leucovorin; CapOx, capecitabine + Oxaliplatin; FUOX, 5-Fluorouracil bolus+ Oxaliplatin.

* See text for details.

require primary prophylaxis, according to the current guidelines.[35,36]

Recently, Alcalay et al. identified a major abdominal surgery, a recent trauma, a colorectal biopsy and a recent medical hospitalisation[37] as risks factors that develop VTE in colorectal cancer patients. Our data strongly suggest that the increased risk is not only linked to cancer itself but there is a strict link between chemotherapy and VTE.

Almost all VTE events (89%) occurred during chemotherapy: 20 out of 27 during FOLFIRI, the remaining 7 during following lines of chemotherapy. The 89% probability that VTE will occur during chemotherapy can be explained by the fact that chemotherapy itself can increase the risk of thromboembolic disease by at least three mechanisms: (1) acute damage on vessel walls; (2) non-acute damage of the endothelium and (3) a decrease in natural coagulation inhibitors (reduced level of C and S proteins with CMF, reduced level of antithrombin III with L-asparaginase).

Levine et al. demonstrated the thrombogenic effect of chemotherapy.[38] They performed a randomised trial comparing 12 weeks of chemo-hormone therapy (using cyclophosphamide, methotrexate, fluorouracil, vincristine, prednisone, doxorubicin and tamoxifen) with 36 weeks of chemotherapy (using cyclophosphamide, methotrexate, fluorouracil, vincristine and prednisone) in patients with stage II breast cancer. Among 205 patients randomly assigned to treatment, there were 14 episodes of thrombosis (6.8%). These 14 episodes occurred during 979 patient-months of chemotherapy; in comparison, there were no events during 2413 patient-months without therapy.

Our data potentially extends these findings and provocatively suggests that reducing the time of exposure to chemotherapy may be a useful strategy to reduce the risk of developing VTE. In our trial, those patients on the intermittent schedule received FOLFIRI every 2 weeks, 2 months on and 2 months off. One may argue that other toxicities have been underestimated; however, a recent clinical trial reported a grade 3/4 toxicity rate very similar to that reported in our trial.[25]

Furthermore, a sequential monochemotherapy, instead of a more toxic combination regimen, is not a useful strategy to reduce vessel damage. In the study reported by Koopman et al.,[25] the incidence of VTE was identical in patients receiving a sequential monochemotherapy and those receiving a

combination of anticancer drugs as the first line chemotherapy in advanced CC patients.

Our data may have potential clinical implication, since there is no evidence that primary prophylaxis is effective in ambulatory GI cancer patients receiving chemotherapy. This is the first time in the literature that similar data have been reported.

Furthermore, most of the events occurred (67%) within 6 months of the onset of treatment. This is in agreement with the data reported for a recent large population-based study.[4] However, the fact that one third of the patients developed VTE during subsequent lines of chemotherapy is not negligible, suggesting that in CC patients the risk of developing VTE remains very high throughout the entire natural clinical history of the disease. This should be considered in clinical practice and in future trials investigating thromboprophylaxis.

Our findings are original for at least two reasons: the first is that the clinical design which allows us to investigate the role of cancer and that of chemotherapy is unique in colorectal cancer patients, and the second is that for the first time in the literature we demonstrate that an intermittent schedule is associated with a reduced risk to develop VTE, highlighting a direct association between chemotherapy and VTE and not just between VTE and cancer. Since chemotherapy can decrease the natural coagulation inhibitors such as Proteins C, S, ATIII, it is not possible to rule out the possibility that, during the 2 months off chemotherapy, these natural inhibitors resumed, thus achieving a correct shift in the balance between anticoagulation and thrombophilic factors. However, we did not evaluate circulating cytokines or proteins related to the coagulation cascade. Further clinical and translational investigations are needed in order to better understand the biological bases of our findings.

During our study, only 2 cases of VTE were spontaneously reported by medical oncologists while, after specifically requesting this analysis, 27 VTE events were retrieved, including 4 episodes of pulmonary embolism. Since our independent study was conducted without local monitoring for toxicities, we hypothesised that these events were missed for reasons strictly related to the study conduction. Our study and the literature review clearly demonstrate that VTE events are under reported in oncology trials despite being a recognised toxicity.

We are not able to completely explain the reasons for this lack of awareness among medical oncologists, we can only hypothesise about it.

First, in its initial version, the US National Cancer Institute Criteria for common toxicity did not include VTE.

Second, the current toxicity definitions with respect to VTE are poor and need clarification. No differences are highlighted between proximal and distal venous thrombosis, although patients with deep vein thrombosis (DVT) of the calf have about half the risk of recurrent VTE as those who have had a proximal DVT. Furthermore, the risk to develop PE is increased for patients with proximal DVT as compared to those with distal DVT. Furthermore, Grade 2 and Grade 3 are strictly related to the need of a therapeutic approach, while there are not so rare clinical situations where oncologist cannot give an active treatment because of thrombocytopaenia or other transient medical conditions.

Finally, no mention is highlighted regarding the fact that in several cases venous thrombosis is a clinically asymptomatic event. In our trial for three asymptomatic patients, a lower vena cava thrombosis was recorded during the restaging of the disease. These events should be carefully checked, since they may be associated with an high risk to develop a severe and potentially fatal PE.

Finally, until 2 years ago no clinical recommendation were produced about VTE by the oncological community. The lack of recommendation sets well the scene regarding the underestimation of this type of toxicity as compared to other toxicities such as nausea, vomiting and anaemia. All these above mentioned reasons may partially justify the underestimation of a severe and potentially fatal complication 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 in order to clarify this issue within the oncology community.

The strength of this study is its relative large cohort of patients, all treated homogeneously, both during the first and second line chemotherapy and with prospective gathering of the relevant data; on the other hand, a limitation is that principally we searched only symptomatic VTE and therefore a number of asymptomatic VTE may have been missed with a consequent underestimation of the risk of VTE. A second limitation is that we describe together catheter-related and lower limbs VTE events, which potentially may have a different pathogenesis.

As far as the potential role of the number of metastatic sites is concerned, due to the lack of other reports, we cannot compare our data. Patients with more extensive disease should be considered a very high risk group for the developing of VTE.

In sum, within a randomised clinical trial, our study showed that (1) VTE is one of the most common and severe complications in advanced CC patients; (2) we clearly demonstrate that there is a strict link between chemotherapy and VTE and not just between VTE and cancer and (3) the intermittent schedule is associated with a reduced risk to develop VTE.

Although this is a potentially fatal complication, this type of toxicity is largely underestimated.

Finally, our clinical findings may have potential impact for daily practice and for the design of future clinical trials.

REFERENCES

1. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;**371**:387–94.
2. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy, an underestimated phenomenon. *Arch Intern Med* 2004;**164**:190–4.

3. Labianca R, Floriani I, Isa L, et al. Alternating versus continuous "FOLFIRI" in advanced colorectal cancer (ACC): a randomized "GISCAD" trial. *Proceedings ASCO*; 2006 [abstract 3505].
4. 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**:458–64.
5. Feliu J, Castañón C, Salud A, Mel JR, et al. Phase II randomised trial of raltitrexed-oxaliplatin vs raltitrexed-irinotecan as first-line treatment in advanced colorectal cancer. *Brit J Cancer* 2005;**93**:1230–5.
6. Van Cutsem E, Dirix L, Van Laethem JL, et al. Optimisation of irinotecan dose in the treatment of patients with metastatic colorectal cancer after 5-FU failure: results from a multinational, randomised phase II study. *Brit J Cancer* 2005;**92**:1055–62.
7. Van Cutsem E, Hoff PM, Harper P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. *Brit J Cancer* 2004;**90**:1190–7.
8. Bajetta E, Di Bartolomeo M, Buzzoni R, et al. Uracil/ftorafur/leucovorin combined with irinotecan (TEGAFIRI) or oxaliplatin (TEGAFOX) as first-line treatment for metastatic colorectal cancer patients: results of randomised phase II study. *Brit J Cancer* 2007;**96**:439–44.
9. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Brit J Cancer* 2006:798–805.
10. Martoni AA, Pinto C, Di Fabio F, et al. Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: a GOAM phase II randomised study (FOCA trial). *Eur J Cancer* 2006;**42**:3161–8.
11. Garufi C, Vanni B, Aschelter AM, et al. Randomised phase II study of standard versus chronomodulated CPT-11 plus chronomodulated 5-fluorouracil and folinic acid in advanced colorectal cancer patients. *Eur J Cancer* 2006;**42**:608–16.
12. Nogué M, Salud A, Batiste-Alentorn E, et al. Randomised study of tegafur and oral leucovorin versus intravenous 5-fluorouracil and leucovorin in patients with advanced colorectal cancer. *Eur J Cancer* 2005;**41**:2241–9.
13. Hospers GAP, Schaapveld M, Nortier JWR, et al. Randomised phase III study of biweekly 24-h infusion of high-dose 5FU with folinic acid and oxaliplatin versus monthly plus 5-FU/folinic acid in first-line treatment of advanced colorectal cancer. *Ann Oncol* 2006;**17**:443–9.
14. Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. *J Clin Oncol* 2006;**24**:3347–53.
15. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005;**23**:4866–75.
16. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;**22**:229–37.
17. Köhne CH, van Cutsem E, Wils J, et al. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol* 2005;**23**:4856–65.
18. Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007;**25**:4779–86.
19. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007;**25**:1670–6.
20. Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. *J Clin Oncol* 2006;**24**:3347–53.
21. Bécouarn Y, Senesse P, Thézenas S, et al. A randomized phase II trial evaluating safety and efficacy of an experimental chemotherapy regimen (irinotecan + oxaliplatin, IRINOX) and two standard arms (LV5 FU2 + irinotecan or LV5 FU2 + oxaliplatin) in first-line metastatic colorectal cancer: a study of the Digestive Group of the Fédération Nationale des Centres de Lutte Contre le Cancer. *Ann Oncol* 2007;**18**:2000–5.
22. Comella P, Massidda B, Filippelli G, et al. Oxaliplatin plus high-dose folinic acid and 5-fluorouracil i.v. bolus (OXAFAFU) versus irinotecan plus high-dose folinic acid and 5-fluorouracil i.v. bolus (IRIFAFU) in patients with metastatic colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase III trial. *Ann Oncol* 2005;**16**:878–86.
23. Kalofonos HP, Aravantinos G, Kosmidis P, et al. Irinotecan or oxaliplatin combined with leucovorin and 5-fluorouracil as first-line treatment in advanced colorectal cancer: a multicenter, randomized, phase II study. *Ann Oncol* 2005;**16**:869–77.
24. Delaunoit T, Goldberg RM, Sargent DJ, et al. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. *Cancer* 2004;**101**:2170–6.
25. Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007;**370**:135–42.
26. Seymour MT, Maughan TS, Ledermann JA, et alFOCUS Trial Investigators; National Cancer Research Institute Colorectal Clinical Studies Group. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;**370**:143–52.
27. Schoemaker NE, Kuppens IE, Moiseyenko V, et al. Randomised phase II multicentre trial of irinotecan (CPT-11) using four different schedules in patients with metastatic colorectal cancer. *Brit J Cancer* 2004;**91**:1434–41.
28. Porschen R, Arkenau HT, Kubicka S, et al. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. *J Clin oncol* 2007;**25**:4217–23.
29. Giacchetti S, Bjarnason G, Garufi C, et al. Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and

oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group. *J Clin Oncol* 2006;**24**:3562–9.
30. Ashley AC, Sargent DJ, Alberts SR, et al. Updated efficacy and toxicity analysis of irinotecan and oxaliplatin (IROX): intergroup trial N9741 in first-line treatment of metastatic colorectal cancer. *Cancer* 2007;**110**:670–7.
31. Díaz-Rubio E, Tabernero J, Gómez-España A, et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. *J Clin Oncol* 2007;**25**:4224–30.
32. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer – a GERCOR study. *J Clin Oncol* 2006;**20**:394–400.
33. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *New Engl J Med* 2000;**343**:905–14.
34. Khorana AA, Francis CW, Culakova E, et al. Risk factors for chemotherapy associated venous thromboembolism in a prospective observational study. *Cancer* 2005;**104**:2822–9.
35. Lyman GH, Khorana AA, Falanga A, 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.
36. Mandala M, Falanga A, Piccioli A, et alWorking Group AIOM. Venous thromboembolism and cancer: guidelines of the Italian Association of Medical Oncology (AIOM). *Crit Rev Oncol Hematol* 2006;**59**:194–204.
37. Alcalay A, Wun T, Khatri V, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. *J Clin Oncol* 2006;**24**:1112–8.
38. Levine MN, Gent M, Hirsh J, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. *New Engl J Med* 1988;**318**:404–7.