Clinical Course of Venous Thromboembolism in Patients with Pancreatic Cancer: Insights from the RIETE Registry

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Thromb Haemost

While numerous studies reported that the risk of venous thromboembolism (VTE) in cancer patients varies widely according to primary cancer site,[1] there is a paucity of data comparing the long-term clinical course of VTE during anticoagulant therapy per site of cancer. Mahé et al recently highlighted that VTE-related outcomes may differ across patients with breast, prostate, colorectal or lung cancer.[2]

Pancreatic cancer (PC) is associated with the highest rates of VTE,[1–6] with an incidence ranging from 5 to 41% in specific PC cohorts,[7–18] and up to 67% in post-mortem series.[19] However, no specific data exist in the literature regarding the risk of recurrent VTE or major bleeding during anticoagulant therapy in PC patients.

Using data from the Registro Informatizado Enfermedad TromboEmbólica (RIETE Registry),[2] we aimed to compare the VTE clinical presentation and outcome during the course of anticoagulant therapy between PC patients and other cancer patients. Rationale, design and methodology of RIETE have been extensively described elsewhere.[20]

Between March 2001 and April 2016, among 10,961 patients with active cancer and acute symptomatic VTE prospectively enrolled in the RIETE Registry, 497 had PC (localized 103, metastatic 394). In the overall studied population, most cancer patients were receiving specific cancer treatment, with either chemotherapy ($n = 5{,}575$ [50.9%]), radiotherapy ($n = 1{,}376$ [12.8%]) and hormonotherapy ($n = 1{,}099$ [10%]) alone or in combination. At time of initial VTE diagnosis, metastatic disease was more frequent in PC than in the other cancer patients ($n = 397$ [79.2%] vs. 5,257 [50.3%]; $p < 0.0001$). More than half of the total number of initial VTE events were pulmonary embolism (PE) ($n = 5{,}699$ [52%]), and the proportions of cancer patients presenting initially with PE did not differ between PC and other cancer patient groups. Compared with other groups, metastatic PC patients who presented a deep vein thrombosis (DVT) initially were more likely to have a proximal DVT. This difference

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versus other groups was statistically significant: $n = 141$ (74%) of all VTE were proximal DVT among metastatic PC patients compared with $n = 31$ (60%) in localized PC, $p < 0.05$; compared with $n = 1,708$ (68%) in other localized cancer patients, $p < 0.0001$; and compared with $n = 1,754$ (71%) in other metastatic cancer patients, $p < 0.0001$. Long-term therapy with low-molecular weight heparin (LMWH) was more frequently used in patients with localized PC ($n = 73$ [74%]) than in those with other localized cancers ($n = 2,579$ [51%]; $p < 0.0001$). Among patients with metastases, there were no differences between patients with PC ($n = 262$ [75%]) or other cancers ($n = 3,436$ [72%]). Fourteen per cent ($n = 14$), 14% ($n = 47$), 17% ($n = 808$) and 35% ($n = 1764$) of them, respectively, switched to vitamin K antagonist (VKA) drugs. Median duration of all types of anticoagulant therapy for VTE was significantly shorter in metastatic PC patients than in other groups ($p < 0.001$), most likely because of their shorter survival.

During the course of anticoagulant therapy, 586 (5.3%) recurrent VTE events ($n = 308$ [52%] DVT and $n = 278$ [48%] PE) occurred in this overall population. The incidence rate (IR) for total recurrent VTE events was non-significantly higher in patients with localized PC than in those with other localized cancers (15.51 events per 100 patient-years [95% confidence interval [CI], 6.22–31.97] vs. 9.58 [95% CI, 8.42–10.85]; p = ns). Metastatic PC patients had a 2.1-fold higher risk for recurrent VTE than other metastatic cancer patients (31.65 events per 100 patient-years [95% CI, 21.03–45.74] vs. 14.70 [95% CI, 13.09–16.45]; $p < 0.001$) (►**Table 1**). On multivariate analysis, in PC patients, hospitalization (hazard ratio [HR], 0.76 [95% CI, 0.62–0.93]; $p = 0.007$), recent surgery (HR, 0.70 [95% CI, 0.54–0.91]; $p = 0.007$), abnormal platelet count at baseline (HR, 1.41 [95% CI, 1.12–1.77]; $p = 0.003$) and metastasis (HR, 2.54 [95% CI, 1.71–3.76]; $p < 0.001$) independently predicted the risk for recurrent VTE.

Major bleeding occurred in 406 patients (4.2%) in the overall cancer population. The IRs for major bleeding were 8.87 (95% CI, 2.39–22.70) in localized PC patients, 15.82 (95% CI, 8.65–26.55) in metastatic PC patients, 6.83 (95% CI, 5.86–7.91) in localized other cancer patients and 12.86 (95% CI, 11.36–14.50) in metastatic other patients (►**Table 1**) and did not significantly differ between groups (p = ns). However, when only considering PC patients, the rate of VTE recurrences during anticoagulation was nearly twofold higher than the rate of major bleeding (26.2 events per 100 patient-years [95% CI, 18.25–36.44] vs. 13.47 events per 100 patient-years [95% CI, 7.98–21.30]). Two hundred and seventy-two PC patients (54%) and 2,816 other cancer patients (25.7%) died during follow-up.

Consistent with a recent analysis of the RIETE database including patients with breast, prostate, colorectal and lung cancer, our results confirm that the clinical course of VTE *differs* according to the primary cancer site. A retrospective cohort of 542 cancer patients (with an unspecified number of pancreas cancer patients) showed that in addition to female gender, previous history of VTE, and TNM stage I/II, lung or breast cancer were clinical predictors of recurrent VTE.[21] Another population-based study showed that brain, lung, ovarian cancer, myeloproliferative or myelodysplastic disorders and PC were associated with an increased hazard of recurrent VTE.[22] In our study, the IR for recurrent VTE in PC patients was 26 (95% CI, 18–36) per 100 patient-years which is higher than in the other studied cancer patients with VTE, and higher than in previous studies in unselected cancer patients,[5] but comparable to the 27 (95% CI, 22–23) per 100 patient-years IR in the RIETE sub-group of lung cancer patients recently analysed.[2]

Long-term treatment with LMWH is the current international standard of care for the treatment of established VTE in cancer patients.[23] A major finding of our study is that PC patients had a higher risk of recurrent VTE and a similar risk

Table 1 Recurrent VTE and other outcomes during the course of anticoagulant therapy

	Non-metastatic pancreatic cancer $n = 103$		Metastatic pancreatic cancer $n = 394$		Non-metastatic other cancers $n = 5,207$		Metastatic other cancers $n = 5,257$	
Years of treatment	45.12		88.47		2,578.16		2,068.32	
Months of treatment	541.43		1,061.67		30,937.90		24,819.87	
Events, per 100 patient-years								
Recurrent DVT	4	8.87 (2.39–22.70)	19	21.5 (12.92–33.54)[a]	136	5.28 (4.43–6.24)	149	7.20 (6.09–8.46)[c]
Recurrent PE	3	6.65 (1.34–19.43)	9	10.17 (4.64–19.31)	111	4.31 (3.54–5.19)	155	7.49 (6.36–8.77)
Recurrent VTE	7	15.51 (6.22–31.97)	28	31.65 (21.03–45.74)	247	9.58 (8.42–10.85)	304	14.70 (13.09–16.45)[c]
Major bleeding	4	8.87 (2.39–22.70)	14	15.82 (8.65–26.55)	176	6.83 (5.86–7.91)	266	12.86 (11.36–14.50)
Overall death	34	75.35 (52.18–105–30)	238	269 (236–306)[b]	688	26.69 (24.73–28.76)[b,c]	2,128	103 (98.0–107)[c]

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
Note: Comparisons were made using patients with pancreas cancer without metastases as reference.
[a] $p < 0.01$.
[b] $p < 0.001$. Comparisons between both pancreas cancer with metastases and other cancers with metastases, and the same cancers without metastases.
[c] $p < 0.001$.

of major bleeding than other cancer patients, thus suggesting the need for intensifying anticoagulation therapy in this setting. While only a trend was observed towards more recurrent VTE events in localized PC patients than in other localized cancer patients, the difference was highly significant for metastatic PC patients. These findings may contribute to better explain why VTE is associated with a shorter overall survival in PC patients,[13,17,24,25] independently of performance status, age or tumor burden.[17] Such high risk of recurrent VTE in PC patients may be related by some primary tumor characteristics including enhanced tissue factor (TF) expression[26] that was demonstrated to play a mechanistic role in the pathogenesis of VTE.[27] Concordantly, a preplanned regression analysis of the CATCH trial[28] recently found that patients in the highest quartile of TF antigen ($>$ 64.6 pg/mL) had an increased risk of VTE (relative risk, 3.3; 95% CI, 2.1–5.1; *p*, 0.001). We also observed a higher rate of recurrent VTE in metastatic PC patients than in their non-metastatic counterparts, consistent with studies showing that metastatic disease is a major risk factor for recurrent VTE.[5,22,29,30]

In recent years, attempts have been made to improve VTE risk stratification in cancer patients. The accuracy and discriminating power of the Ottawa score to predict the risk for recurrent VTE in cancer patients[21] appeared modest in a retrospective study using data from the RIETE registry.[31] All together, these data highlight the need for new prediction tools necessarily including the various cancer types and their dissemination status.

In summary, our results confirm that the clinical course of VTE *differs* according to the primary cancer site. New scores to predict the risk for recurrent VTE in patients with cancer-associated thrombosis should include all cancer types and dissemination status. Further studies evaluating the benefit and risk of specific anticoagulant strategies according to the primary cancer site are warranted.

Authors' Contributions

C.F., D.F. and M.M. designed the study. C.F., Á.S., R.Q., J.G.-M., F.J.V. and J.L. included patients and collected data. C.F., J.T.-S., D.F. and M.M. analysed the data. C.F., D.F. and M.M. drafted the manuscript. All authors revised the manuscript and agreed to the final version.

Conflict of Interest

None.

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