Risk of venous thrombosis in patients with pancreatic adenocarcinoma

Emmanuel MITRY (1, 4), Raffic TALEB-FAYAD (1), Antoine DESCHAMPS (2, 4), Nicolas MANSENCAL (3, 4), Céline LEPÈRE (1), Gilles DECLETY (1), Astrid LIÈVRE (1, 4), Jean-Nicolas VAILLANT (1), Gilles LESUR (1), Élisabeth CRAMER (2, 4), Olivier DUBOURG (3, 4), Philippe ROUGIER (1, 4)

(1) Service d’hépatogastroentérologie et oncologie digestive ; (2) Service d’hémato-oncologie ; (3) Service de cardiologie, Hôpital Ambroise-Paré, APHP, Boulogne ; (4) Université Versailles Saint-Quentin, UFR de médecine Paris-Ile-de-France-Ouest.

SUMMARY

Aim — To estimate the risk of venous thrombosis associated with pancreatic adenocarcinoma and its consequences on treatment and survival.

Patients and methods — We retrospectively analyzed a cohort of 90 patients (49 males, 41 females — median age: 67 years [range: 37-94]). Pancreatic adenocarcinoma was histologically proved in 72 patients (81%) and was metastatic in 49 patients (54.4%). A venous thrombosis was observed in 24 patients (26.7%). A pulmonary embolism occurred in 4 patients with 2 deaths. The risk of venous thrombosis was significantly reduced by the use of antithrombotic prophylaxis (HR: 0.03 [95CI:0.003-0.27]) and increased among patients with a biological inflammatory syndrome (HR: 9.0 [95CI:2.30-34.4]) and metastatic disease (HR: 4.4 [95CI:1.1-17.9]). Overall survival was not different between patients with (6.6 months) or without (6.1 months) venous thrombosis.

Conclusion — The risk of venous thrombosis is important and may delay the treatment in patients with advanced pancreatic carcinoma. Some patients with high risk of venous thrombosis may benefit from a prophylactic anticoagulant treatment.

RÉSUMÉ

Risque de thrombose veineuse chez les malades porteurs d’un adénocarcinome pancréatique

Emmanuel MITRY, Raffic TALEB-FAYAD, Antoine DESCHAMPS, Nicolas MANSENCAL, Céline LEPÈRE, Gilles DECLETY, Astrid LIÈVRE, Jean-Nicolas VAILLANT, Gilles LESUR, Élisabeth CRAMER, Olivier DUBOURG, Philippe ROUGIER

(Objectifs — Estimer le risque de thrombose veineuse chez les malades présentant un adénocarcinome du pancréas et ses conséquences sur le traitement et la survie.

Malades et méthodes — Nous avons rétrospectivement analysé une cohorte de 90 malades (49 hommes, 41 femmes — âge médian 67 ans [extrêmes : 37-94]). L’adénocarcinome pancréatique était prouvé histologiquement chez 72 malades (81 %) et métastatiques chez 49 malades (54,4 %).

Résultats — Une thrombose veineuse a été observée chez 24 malades (26.7 %). Une embolie pulmonaire est survenue chez quatre malades entraînant deux décès. Le risque de thrombose veineuse était significativement réduit par l’utilisation d’un traitement anticoagulant prophylactique (HR : 0,03 [IC95 : 0,003-0,27]) et augmenté chez les malades présentant un syndrome inflammatoire biologique (HR : 9,0 [IC95 : 2,30-34,4]) ou une maladie métastatique (HR : 4,4 [IC95 : 1,1-17,9]). La survie globale n’était pas différente chez les malades avec (6,6 mois) ou sans (6,1 mois) thrombose veineuse.

Conclusion — Le risque de thrombose veineuse est important et peut retarder la prise en charge des malades ayant un adénocarcinome pancréatique avancé. Certains malades à haut risque de thrombose veineuse pourraient bénéficier d’un traitement anticoagulant prophylactique.

Introduction

The risk of deep venous thrombosis (DVT) is particularly high in patients with cancer, especially advanced-stage (metastatic or locally invasive) pancreatic cancer where estimates reach 20-25% [1, 2]. The consequences of this serious complication can have a significant impact on therapeutic management, patient survival, and quality of life.

Patients and methods

This retrospective analysis concerned 90 patients treated in our university hospital between January 1998 and June 2001. The following data were collected from the patient files retrieved from the hospital’s...
patient group database (PMSI\(^1\)): medical history, clinical features, laboratory results, pathology findings (tumor histology, localization, stage), treatments.

The diagnosis of adenocarcinoma of the pancreas was proven (pathology for 72 patients) or highly probable because of the clinical manifestations associated with a highly suggestive aspect on the computed tomography and elevation of serum CA19-9 (>300 IU/mL, N=18 patients).

The clinical suspicion of DVT was confirmed by duplex Doppler (venous incompressibility) \([3]\). The presence of a thrombus on the thoracic angioscan confirmed the diagnosis of PE \([4]\). During the study period, duplex Doppler and thoracic angioscan were not systematic explorations in the unit but were ordered for patients with a suggestive clinical presentation.

### Statistical analysis

Fisher’s exact text was used to compare proportions. Multivariate analysis with logistic regression was used to search for factors associated with the development of DVT and survival was determined with the Kaplan Meier method. Data analysis was performed with Stata software (Intercooled Stata 9.2 for Windows. StataCorp LP, College Station, TX 77845 USA).

### Results

#### Population

Median age of the 90 patients (49 male, 41 female) was 67 years (range 37-94 years). One patient with operated arteritis of the lower limbs was on oral anticoagulant prophylaxis at an effective dose. Four patients (4.4%) had a history of DVT and 25 patients (27.8%) had a subcutaneous venous access for chemotherapy. There was no evidence of familial history of thrombophilia in any of the patients, but all data were collected retrospectively from medical files.

The tumor was located in the head of the pancreas (N=59), the body (N=6), the tail (N=21) or unknown (N=4). Metastatic spread was noted in 49 patients (54.4%) to the liver (N=48), the lung (N=1) and bone (N=4). Thirteen patients (14.4%) presented a recurrent tumor after primary potentially curative resection.

Laboratory tests showed signs of inflammation (elevated serum levels of inflammatory proteins) in 34 patients (37.8%), but data were missing for nine patients (10%). Treatment included surgery (42.2% of patients), chemotherapy (55.5%) for metastatic tumor (61.2%) and locally invasive tumor (48.8%), and radiotherapy (17.7%) for metastatic tumor (8.2%) and locally invasive tumor (29.3%).

#### Deep vein thrombosis

DVT was observed in 24 patients (26.7%) who presented DVT of the peripheral veins of the lower limbs (N=22 patients) and venous thrombosis of the subcutaneous venous access site (N=4 patients). Two patients had both. DVT of the lower limbs was bilateral in four patients. PE was noted in four patients (4.4% of the study population) who had a DVT of the lower limbs. The PE was bilateral in three patients and recurrent in one.

In five patients, the DVT was identified before the diagnosis of pancreatic adenocarcinoma (mean time interval 15 days, range 1-85 days) and was considered as the inaugural sign of the later. For 19 other patients, the DVT was identified after the diagnosis of pancreatic adenocarcinoma (mean time interval 96 days, range 4-492)

All patients were treated with curative doses of low-molecular-weight heparin (LMWH) initiated at diagnosis of DVT (including the one patient on oral anticoagulants). For three patients with a subcutaneous thrombus, the oral anticoagulation therapy was continued after discontinuation of the heparin. For the other patients, LMWH was continued as a long-term treatment.

### Facteurs associés avec la thrombose

Among the 29 patients (32.2% of the study population) given LMWH as preventive treatment, one (3.4%) developed DVT. Among the 61 patients not given prophylactic LMWH, 23 (37.7%) developed DVT. The difference was significant (P=0.004). DVT was observed in 38.8% (19/49) of patients with a metastatic tumor compared to 12.2% (5/41) with non-metastatic disease (P=0.005). The risk of DVT was also higher in patients with biological signs of inflammation: 25.9% (15/34) versus 12.8% (6/47), P=0.001 and in patients given chemotherapy: 36% (18/50) versus 15% (6/40), P=0.03.

Gender, tumor localization, presence of a personal history of DVT, or presence of a subcutaneous venous access, surgery, or radiotherapy were not significantly associated with a higher risk of DVT.

At multivariate analysis, anti-coagulant prophylaxis (OR=0.03), inflammation (OR=9.0), and metastatic disease (OR=4.4) were significantly linked to the risk of DVT (table I). At multivariate analysis, chemotherapy was not associated with a higher risk of DVT.

### Consequences of DVT on patient management and survival

The development of DVT requiring institution of curative dose anticoagulation led to a change in the therapeutic management of the pancreatic tumor, in comparison with the initially planned treatment, in 7/24 patients (29.2%). Chemotherapy had to be discontinued earlier than planned in three patients (including one whose subcutaneous venous access had to be removed). Onset of chemotherapy was retarded in two patients and in two others could not be instituted before death due to PE.

Median patient survival for the entire population was 6.4 months (CI95: 4.1-7.6). Median survival was not significantly different between patients with (6.6 months, CI95: 3.7-11.1) or without thrombosis (6.2 months, CI95: 3.8-7.6) (figure 1).

### Discussion

Cancer is a well-documented cause of acquired thrombophilia. Clinical manifestations of cancer-induced thrombophilia include microthrombosis in disseminated intravascular coagulation or thrombotic microangiopathy, arterial thrombosis, and particularly venous thrombosis \([5]\). The pathogenic mechanisms

---

\(^1\) Programme de médicalisation du système d’information.
underlying these complications are both complex and multifactorial [6]; tumor growth can have a direct or indirect effect in addition to the potentially thrombogenic effect of anti-tumor treatments (chemotherapy and hormone therapy, surgery, catheter insertion). Diverse coagulation disorders have been reported in these patients involving plasma coagulation, fibrinolysis, and platelet dysfunction [6, 7]. The pro-thrombotic effect of tumor cells leads to and maintains a state of hypercoagulability demonstrated by the commonly observed increase in markers of coagulation activation such as fibrinopeptide A, prothrombin fragments 1+2, thrombin-antithrombin (TAT) complex or fibrin degradation products (FDP) [8]. Nevertheless, to date, the predictive value of these anomalies in terms of venous thrombosis remains to be clearly demonstrated [9]. In addition to changes associated with tumor growth, the presence of a predisposing genetic anomaly (Leiden factor V, mutation of the prothrombin gene G20210A) can further increase the risk of thromboembolism [10, 11].

Advanced-stage pancreatic cancer is known to be particularly thrombogenic; venous thrombosis is frequent in these patients [1, 2].

Our retrospective analysis included 90 patients treated for adenocarcinoma of the pancreas during a four year period (1998-2001). Slightly more than half of the patients had a metastatic tumor, the others presenting a non-metastatic but unresectable tumor because of local invasion. DVT occurred in 24 patients (26.7%); this occurred before discovery of the pancreatic tumor in five (5.6%) patients. The risk of DVT was greater in patients with a metastatic tumor (38.8%) than in those with a locally invasive tumor (12.2%). In our series, DVT of the lower limbs was probably favored by tumor compression of the inferior vena cava for one patient.

The results of this study are in agreement with data reported in the literature and with the incidence of DVT among patients with a malignant pancreatic tumor which have varied from 11 to 57% in retrospective reports [2, 12-14]. Prospective data are scarce [1]. Blom et al. reported that thrombosis formation was associated with chemotherapy, tumor localization in the body or tail and metastatic spread [2]. The risk was also particularly high in the postoperative period [2].

In one recent therapeutic trial evaluating chemotherapy with a gemcitabine, docetaxel, capecitabine combination for the treatment of advanced-stage pancreatic adenocarcinoma, the incidence of DVT was 15% among patients with locally advanced disease and 26% among those with metastatic disease [1].

Conclusion

The development of DVT in cancer patients can have a major impact on therapeutic management as well as patient survival and quality of life. Chemotherapy may have to be discontinued or retarded, particularly if the thrombus affects the subcutaneous venous access site. In our study, two patients died from PE complicating DVT and anti-tumor treatment had to be interrupted in seven (29.2% of the patients with DVT). DVT can also be associated with poor quality of life and patient discomfort. This can have a major impact since optimal quality of life is an essential therapeutic objective for patients with advanced-stage pancreatic cancer. In our series, DVT was not associated with shorter survival, probably because effective curative treatment was instituted.

Anti-thrombotic prophylaxis might be proposed for patients with a high risk of developing DVT. In our study, anti-thrombotic prophylaxis was significantly associated with a lower risk of DVT, while metastatic spread and biological inflammation were associated with higher risk. Nevertheless, systematic prophylaxis cannot be recommended due to the lack of evidence demonstrating its beneficial effect [15, 16]. However, we suggest that it could be indicated in patients with a metastatic tumor and/or biological signs of inflammation.

REFERENCES

