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Full Length Article

Incidence, outcome and risk stratification tools for venous thromboembolism in advanced pancreatic cancer – A retrospective cohort study

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is frequent in advanced pancreatic cancer (APC). Recent studies demonstrated that the Khorana score - an established risk stratification tool for VTE in cancer - performs poorly in identifying pancreatic cancer patients at high risk for VTE.
Materials and methods: We performed a retrospective cohort study in order to define incidence, treatment and outcome of VTE as well as the performance of VTE risk stratification tools (Khorana score, CONKO score and aPTT ratio) in a "real life" clinical cohort of APC patients undergoing palliative chemotherapy.
Results and conclusions: One hundred and seventy-two eligible APC patients from our comprehensive cancer center were identified. VTE after start of palliative chemotherapy was diagnosed in 71 patients (41.3%). Most VTE events were asymptomatic ($n = 50$, 29.1%) with only 21 symptomatic events (12.2%). On multivariate analysis - including age, performance status and carbohydrate antigen 19-9 (CA 19-9) - symptomatic VTE was an independent risk factor for death (hazard ratio [HR]: 2.22, 95% CI: 1.05–2.60, $p < 0.05$). Khorana score, CONKO score and aPTT ratio alone were not able to predict the risk for symptomatic VTE. High risk patients could only be identified by using a combination of either Khorana or CONKO score with aPTT ratio (30% vs. 10% symptomatic VTE events in high vs. low risk patients, $p < 0.05$). The combination of Khorana or CONKO score with aPTT thus may represent a novel risk stratification tool for symptomatic VTE in APC and should further be validated within prospective clinical trials.

1. Introduction

Venous thromboembolism (VTE) represents a frequent complication in advanced pancreatic cancer (APC) patients with an estimated incidence between 12.1 and 42% [1–4]. Prophylactic use of anticoagulation in ambulatory patients with APC remains controversial: recent randomized controlled trials reported that the prophylactic use of low molecular weight heparin (LMWH) can efficiently reduce symptomatic VTE events in ambulatory patients with APC [5,6]. Yet, the impact of LMWH prophylaxis on patient outcome in terms of quality of life (QoL) and overall survival (OS), as well as optimal dosing of LMWH in ambulatory patients with APC, are still a matter of debate [7]. Further, selection of high risk patients who might derive the highest

Abbreviations: APC, advanced pancreatic cancer; aPTT, activated partial thromboplastin time; CA 19-9, carbohydrate antigen 19-9; HR, hazard ratio; KPS, Karnofsky performance status; LMWH, low molecular weight heparin; OS, overall survival; PC, pancreatic cancer; QoL, quality of life; SVT, splanchnic vein thrombosis (SVT); VTE, venous thromboembolism.

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benefit from LMWH is difficult in APC. The Khorana score was developed to identify cancer outpatients with a high risk of VTE [8]. Patients are stratified into three risk categories for VTE (low, intermediate and high risk) according to five patient characteristics (site of cancer, platelet count, hemoglobin level or erythropoietin use, leukocyte count and presence of obesity) [8]. As obesity is rare in patients with APC, the CONKO group suggested replacing body mass index by performance status [9]. As reported very recently, the Khorana score performs poorly in identifying pancreatic cancer (PC) patients with a high risk of VTE, while to the best of our knowledge, the CONKO score has not been validated in an independent patient cohort yet [10].

In formerly healthy subjects, an activated partial thromboplastin time (aPTT) below the median has been shown to serve as an independent predictor for future development of VTE [11,12]. For patients with different types of cancer the risk of a catheter-associated venous thrombosis also increases with a shorter aPTT [13]. Further, in a large prospective cohort study including 1869 patients with a variety of cancers, a shorter aPTT was associated with an increased VTE risk, independently of tumor site and results of further coagulation studies such as D-dimer or factor VIII [14].

We therefore performed a retrospective cohort study at a single high-volume comprehensive cancer center on VTE in APC to define incidence, treatment, and outcome of VTE events as well as the performance of different VTE risk stratification tools in a "real life" clinical setting.

2. Patients and methods

2.1. Patient selection

Our prospectively maintained outpatient database was used to identify adult patients who presented at our comprehensive cancer center with a histologically or cytologically confirmed diagnosis of metastatic or locally advanced PC from 2002 onwards. Only patients who received treatment at our cancer center were included in the present analysis. Insufficient data quality precluded inclusion in our study cohort. Further exclusion criteria were: endocrine neoplasms of the pancreas, second malignancy other than PC and more than three lines of adjuvant or neoadjuvant treatment for resectable PC before diagnosis of APC. The following patient and tumor characteristics were analyzed for the current study: age; sex; Karnofsky performance status (KPS); tumor-, node-, metastases- (TNM) stage; grading; date of initial diagnosis of PC and treatment of PC. Information on VTE prior to initiation of palliative treatment and occurrence of VTE were retrieved retrospectively from individual medical patient records. Likewise information on bleeding events and outcome of bleeding were recorded. Further we gathered information on preexisting and newly initiated treatment with anticoagulants at initiation of palliative therapy as well as during palliative treatment. Incidence of symptomatic VTE was correlated to Khorana score, CONKO score and activated partial thromboplastin time (aPTT) ratio in patients that were not treated with anticoagulants at time of initiation of palliative treatment. Survival status was determined by (a) review of medical records at our institution, (b) consultation of patient's primary care physician or (c) consultation of patient's civil registrar office. Database lock was in 2012. This study had approval from the local ethics committee of Ludwig-Maximilians-University of Munich (approval number 067-11).

2.2. Calculation of Khorana and CONKO score

Khorana score and CONKO score were calculated as described previously [8,9]: To calculate the Khorana score, one point each was given for thrombocytosis (platelet count of 350 G/L or more), anemia (hemoglobin <10 g/dL and/or use of erythropoiesis-stimulating agents), leukocytosis (leukocyte count >11 × G/L) and obesity (body mass index of 35 kg/m^2 or more). In the original Khorana score, additional points are given depending on the primary site of cancer (one point for "high risk cancer site" (1 point) or two points for "very high risk cancer site"). As pancreatic cancer was defined as a "very high risk site" in the original publication by Khorana et al., minimum score in our patient cohort was 2 points. Depending on the total score, APC patients in our cohort were grouped in Khorana "intermediate risk" (2 points) or "high risk" (>2 points). To calculate the CONKO score, obesity was removed from the Khorana score and replaced by Karnofsky-Performance Status (KPS) (one point for KPS ≤ 70%). Patients were then grouped in CONKO "intermediate risk" (2 points) or "high risk" (>2 points).

2.3. Statistical analyses

OS from the time of initiation of first-line palliative treatment to the time of death from any cause was calculated using the Kaplan-Meier method; differences between groups were analyzed using the hazard ratio (HR) with 95% confidence intervals (95% CI) and the log-rank test. Multivariate analysis to identify prognostic factors for overall survival in our cohort included the following covariates: age, Karnofsky performance status ≤ 70%, use of LWMH in prophylactic dosage (all patients receiving LWMH in prophylactic dosage at time of initiation of palliative therapy were included - independent of the presence of a prior VTE in the patient's history), symptomatic VTE during palliative chemotherapy, VTE prior to palliative chemotherapy and CA 19-9 (log U/ml). To test for the performance of CONKO-score, Khorana-score and aPTT-ratio in predicting a symptomatic VTE, contingency tables and the chi-squared test were used. SPSS PASW 23.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analyses. For this study, a p-value of ≤0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

One hundred and seventy-two APC patients were identified who met the inclusion criteria outlined above. A majority of patients was male (59%; $n = 102$); had a good performance status (KPS 90 to 100: 72% or $n = 123$) and metastatic disease (80%; $n = 137$) (Table 1). Histology was pancreatic ductal adenocarcinoma in 97% ($n = 166$), acinar cell carcinoma in 2% ($n = 4$) and not further specified in two cases (cytology only). Most patients received gemcitabine or gemcitabine-based combination chemotherapy as first-line treatment (69%; $n = 118$) (Table 1). At the time of final analysis, 164 of the 172 patients (95.3%) had died; median OS in the entire cohort was estimated with 9.2 months (95% CI: 7.4–11.0 months).

3.2. Venous thromboembolic events prior to initiation of palliative first-line therapy

Data on VTE prior to initiation of palliative therapy was available for 127 of 172 patients (74%): 47 patients (37%) had a history of VTE, with most events (89%, $n = 42$) occurring one year or less prior to diagnosis of PC (Table 2). Of note, splanchnic vein thrombosis (SVT) accounted for the majority of these events ($n = 29/42$) followed by pulmonary embolism and deep vein thrombosis of the lower extremity (11 and 10 cases respectively, more than one location possible). No survival difference was found for patients with or without VTE prior to initiation of palliative therapy (median OS 7.1 vs. 9.9 months, $p = 0.16$; Fig. 1a and Table 2).