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High prevalence of incidental and symptomatic venous thromboembolic events in patients with advanced pancreatic cancer under palliative chemotherapy: A retrospective cohort study

Anne Katrin Berger, MD [a, *], Hans Martin Singh, MD [a], Wiebke Werft, PhD [b], Alexander Muckenhuber, MD [c], Martin R. Sprick, PhD [d, e, f], Andreas Trumpp, PhD [d, e, f], Wilko Weichert, MD [c], Dirk Jäger, MD [a], Christoph Springfeld, MD, PhD [a]

[a] National Center for Tumor Diseases (NCT), Department of Medical Oncology, University Hospital Heidelberg, Heidelberg, Germany
[b] Hochschule Mannheim, University of Applied Sciences, Mannheim, Germany
[c] Institute of Pathology, Technische Universität München (TUM), München, Germany
[d] Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM), Heidelberg, Germany
[e] Division of Stem Cells and Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany
[f] German Cancer Consortium (DKTK), Heidelberg, Germany

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ABSTRACT

Objectives: Pancreatic cancer patients are at high risk for venous thromboembolic events (VTEs), and chemotherapy is a known additional risk factor. In this context, there is a controversial discussion whether prophylactic anticoagulation should be offered to all outpatients receiving chemotherapy.
Methods: In this retrospective study, we analyzed incidental and symptomatic VTEs in 150 pancreatic cancer patients receiving either gemcitabine-based chemotherapy or chemotherapy according to the FOLFIRINOX protocol.
Results: VTEs were identified in 25% of patients, but were not associated with an adverse survival. There was no significant difference in VTE incidence between patients treated with gemcitabine-based chemotherapy or the more intensive FOLFIRINOX protocol. A commonly used risk score to predict VTEs in cancer patients did not predict the occurrence of VTEs in our patients. The occurrence of VTEs was not associated with one of the recently described pancreatic cancer subtypes.
Conclusion: One quarter of pancreatic cancer patients treated with palliative chemotherapy develops symptomatic or incidental VTEs that cannot be predicted by type of chemotherapy, subtype of pancreatic cancer or a commonly used risk score. Further studies are necessary to identify patients at risk, and to better define which patients at risk should be treated with prophylactic anticoagulation.

Introduction

Pancreatic adenocarcinoma is the fourth common cause of cancer-related death in the Western World [1]. Due to the tumor's aggressive biology, most patients are either primarily diagnosed with advanced disease (APC, advanced pancreatic cancer), or they relapse after curatively-intended surgery. Thus, systemic palliative treatment is needed for the majority of patients. Even with the most modern antineoplastic regimens, however, the median overall survival for APC does not exceed 12 months [2,3]. Recently, biologically distinct subtypes of pancreatic cancer with prognostic and maybe also therapeutic significance have been identified [4,5], but this has not yet resulted in clinical consequences.

Besides its desperate prognosis, APC is one of the malignancies with the highest incidence of venous thromboembolic events (VTEs) [6,7]. VTEs are known as an independent negative prognostic factor in cancer patients [8]. Aside from the type of the primary tumor and patient-related factors such as medical comorbidities, known risk factors include metastatic compared to limited disease and the use of systemic antineoplastic treatment [6,9,10]. For APC, the frequency for symptomatic VTEs under

* Corresponding author. Department of Medical Oncology, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany.
E-mail address: anne.berger@med.uni-heidelberg.de (A.K. Berger).

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chemotherapy is reported to be between 15 and 20% [11–13], and up to 35% including both incidental and symptomatic events [14]. A strong association of VTEs with a poor prognosis was found to be independent of clinical symptoms in APC and other cancers [14–16]. Aside from a meaningful clinical impairment, VTEs additionally cause prolonged hospitalization and a considerable increase of health costs [11,17]. Whereas there is a strong recommendation for VTE prophylaxis for hospitalized cancer patients and in the perioperative period, the question whether cancer patients should be treated with prophylactic anticoagulation is not answered sufficiently in the outpatient setting. Currently, prophylaxis is only recommended for *high-risk* patients [18]. Recently, the phase III CONKO-004 trial provided some evidence, that in ambulatory patients with APC, symptomatic VTEs can be prevented by prophylactic low-molecular weight heparin with a favourable toxicity profile but without impact on survival times [13]. However, it still remains controversial, if all outpatients with APC should receive VTE prophylaxis [19].

Considering VTEs and their management (prophylaxis as well as treatment) as a frequent and meaningful clinical question in APC patients, we aimed to analyze the prevalence of incidental and symptomatic VTEs in a non-trial patient cohort, reflecting a representative cross section of oncological routine APC patients. We therefore retrospectively analyzed 150 patients who started palliative first-line treatment with either FOLFIRINOX or gemcitabine-based at the outpatient clinic of the National Center for Tumor Diseases (NCT) at Heidelberg University Hospital and investigated the frequency, characteristics, treatment and outcome of VTEs in academic practice.

Patients and methods

Patients

For this analysis, requirements for inclusion were (1) histologically proven diagnosis of ductal pancreatic adenocarcinoma, (2) irresectable (metastasized or locally advanced) disease and (3) start of palliative first-line treatment with either FOLFIRINOX between January 2010 and June 2014 or gemcitabine-based therapy (GEM) between January 2007 and December 2011 at the NCT Heidelberg, Germany. The data were maintained via a prospective database, the *NCT clinical cancer registry*. The observation period for each patient started with initiation of first-line treatment (i.e. first systemic chemotherapy after primary diagnosis of metastatic or inoperable disease or, in resected patients, after diagnosis of recurrence**).** The follow-up period for this analysis ended on November 15th, 2015. Survival data were available for 143 patients (95%) for overall survival (OS) and for 150 patients (100%) for progression-free survival (PFS).

Assessment

The clinical data were reported via an electronic medical record by the attending oncologists and medical staff. Information included Eastern Cooperative Oncology Group performance status (ECOG PS) [20], presence and site of metastases at diagnosis, date of previous surgery and adjuvant chemotherapy, start and stop date of chemotherapy, type and severity of toxicities, response to first-line therapy, date of progression, and date of death. Side effects were registered according to the US National Cancer Institute's common terminology criteria for adverse events (CTCAE). Tumor response was routinely evaluated according to the response evaluation criteria in solid tumors (RECIST [21]). Standard staging consisted of a CT scan of thorax, abdomen and pelvis including a venous phase. Incidental and symptomatic VTEs Grade 2 or higher were identified using the medical record and the radiology reports and were systematically analyzed. The Khorana Score (KS [22]) was retrospectively calculated and included the predescribed variables a) site of cancer (2 points for APC), b) prechemotherapy platelet count (1 point if $\geq$ 350/nl), c) hemoglobin level (1 point if < 100 g/l), d) prechemotherapy leukocyte count (1 point if > 11/nl) and e) body mass index (1 point if $\geq$ 35 kg/m^2).

Immunohistochemistry

All immunohistochemical stainings were done on whole tissue slides by hands of a seasoned technical assistant after unmasking of epitopes by boiling in citrate buffered distilled water (pH 6) for 15 min in a pressure cooker (30 min cooldown) using the Dako REAL™ peroxidase detection system kit with included ready to use anti-rabbit/mouse secondary antibody according to the manufacturers specifications (Catalog No. K5003). Primary antibodies used were rabbit polyclonal anti-HNF1 antibody (Catalog Nr. sc-8986) at a dilution of 1:100 and mouse monoclonal anti-KRT81 antibody (Catalog Nr. sc-100929) at a dilution of 1:500, both by Santa Cruz Biotechnology Inc. (Dallas, Texas, U.S.A.). Immunohistochemical stainings were evaluated by a seasoned pathologist to assess Collision-subtypes as performed in previously published works [5]. Nuclear staining of HNF1 at medium or high intensity was considered a biologically relevant HNF1-overexpression and cases were classified as exocrine subtype. For KRT81 a cutoff of >10% of tumor cells was introduced to avoid overinterpretation of single budding KRT81 positive tumor cells at the invasive front and cases with >10% KRT81 positive tumor cells were classified as quasi-mesenchymal subtype. If both stainings were negative cases were classified as classical subtype. In the rare case of double-positive staining, cases were considered quasi-mesenchymal as survival was comparably poor indicating a similar biological phenotype.

Statistical analysis

PFS was defined as the time from start of treatment to documented tumor progression or death. OS was defined as the time from start of treatment to death. Fisher's exact test and Kruskal Wallis test were used for comparing independent samples of categorical and continuous data, respectively. For the association of the Khorana score and the histological subtype, respectively, with the time from start of treatment until the occurrence of VTE a cause specific hazard approach has been considered [23]. Death is defined as competing risk for the occurrence of VTE. For these analyses, 7 patients whose VTE occurred before start of chemotherapy were defined as event free at the start of treatment. Group comparisons were analyzed with the log rank test for the cause of VTE. For both covariates cumulative incidence rates were plotted including 95% confidence intervals. To test the influence of VTE on OS, a Cox proportional hazards model was used including VTE as time-dependent covariable [24]. Additionally, two subgroups of VTEs were defined and their impact on OS was analyzed: VTEs of the extremities together with pulmonary embolism and visceral VTEs together with port-catheter-related events, the latter group considered as “atypical” and rather associated with mechanical factors such as tumor-stenosis and foreign-body-implementation than primarily dysfunction of coagulation. Estimated survival probabilities for VTE and non VTE were obtained by the Simon and Makuch method. All *P*-values were two-sided. *P*-values <0.05 were considered statistically significant. No correction for multiple testing was performed. All analyses were carried out with software R, version 3.2.1 (R Foundation, Vienna, Austria).

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