Cancer-associated venous thromboembolism: unfolding the role of the intrinsic coagulation pathway

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Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54025

Source
ToetsingOnline

Brief title
CELESTA study

Condition

- Gastrointestinal neoplasms malignant and unspecified
- Embolism and thrombosis

Synonym
blood cloth, cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Intrinsic coagulation pathway, Neoplasms, Venous thromboembolism

Outcome measures

Primary outcome

The primary outcome is the level of factor IXa-antithrombin (FIXa:AT). The FIXa:AT complex reflects an early part of the coagulation cascade, and relatively late part of the intrinsic coagulation pathway, immediately prior to factor X and prothrombin conversion. FIXa:AT thereby provides the most accurate estimation of intrinsic pathway activation.

Secondary outcome

Secondary study outcomes are:

1. Factor XIIa-, factor XIa-, and kallikrein (PKa)-inhibitor complexes: FXIIa-C1inh, FXIIa:AT, FXIa-C1inh, FXIa-AT, FXIa:a1AT, and PKa:C1inh complexes

2. FXIa-dependent thrombin generation test

3. Cancer-related activators of the intrinsic pathway: NET-formation markers (myeloperoxidase, nucleosomes, and citrullinated histone H3), cell-free DNA and polyphosphate extracellular vesicles

4. Extrinsic pathway activation and cancer-related activators: FVIIa-AT complexes and TF extracellular vesicles.

See protocol section 5.1.2 for details.

Study description

Background summary

Patients with cancer have a 9- to 20-fold higher risk of venous thromboembolism (VTE) compared with patients without cancer. Despite adequate anticoagulant therapy (e.g. with direct oral anticoagulants [DOACs] and low-molecular-weight heparin [LMWH]), the risk of recurrent VTE and bleeding is much higher in these patients than in VTE patients without cancer. Recent trials comparing DOACs with LMWH in cancer patients have reported a 6-month risk of about 8% for recurrent VTE, and 6% for major bleeding.

The extrinsic coagulation pathway was long thought to be the main driver of VTE in cancer patients. However, recent evidence suggests that the intrinsic coagulation pathway may play an important role as well. The extrinsic pathway is initiated by the complex of tissue factor (TF) and plasma factor VII/VIIa (TF-FVIIa), which subsequently activates FIX and finally way the common pathway. The intrinsic pathway is initiated through activation of FXII. FXIIa will subsequently activate FIX and FX, through FXIa and kallikrein (KAL), which will ultimately lead to thrombin generation. Increasing data suggest that the intrinsic pathway is activated in patients with cancer. Campello et al. compared the coagulation profile of 104 patients with cancer-associated VTE and 555 patients with VTE not related to cancer. Factor XI levels were found to be higher in patients with cancer-associated VTE (127 ± 33% vs. 119 ± 32%, p = 0.042), suggesting a potential role of the intrinsic pathway in cancer-associated VTE. Previous small case-control studies have reported similar findings on higher intrinsic pathway activation in cancer patients without VTE compared with healthy controls. However, these studies were limited by a lack of standardized measures to assess intrinsic pathway activation. Assessing activation of intrinsic coagulation is limited to quantification of enzyme:inhibitor complexes due to the lack of assays for free coagulation enzymes. Furthermore, there are currently no data on the difference of intrinsic pathway activation between cancer patients with and those without VTE, which renders the role of the intrinsic pathway in cancer-associated VTE uncertain. Several studies have reported on potential mechanisms that can lead to intrinsic pathway activation in cancer patients specifically. For example, neutrophil extracellular traps (NETs), cell-free DNA (cfDNA), and polyphosphate-bearing extracellular vesicles were shown to induce VTE in cancer patients in an intrinsic pathway-dependent manner.

Low-molecular weight heparins and DOACs mainly target the common coagulation pathway (factor Xa and IIa). In the past few years, several drugs have been developed that target the intrinsic pathway. An open-label phase II study in patients undergoing knee arthroplasty demonstrated that FXI antisense oligonucleotide (hepatic FXI synthesis inhibitor) 300 mg dosed once was more effective than standard-of-care enoxaparin (LMWH) once daily (VTE risk 4% vs. 30%) with less bleeding (3% vs. 8%). We hypothesize that the intrinsic pathway plays a prominent role in cancer-associated VTE, and that novel intrinsic pathway inhibitor might be especially efficacious in cancer patients, while mitigating their high risk of bleeding. Before using such agents in this high-risk population, it is crucial to get better understanding of the

underlying role of the intrinsic pathway in development of VTE in cancer patients.

Study objective

The primary aim of this study is to compare intrinsic pathway activation between cancer patients with acute VTE and those without VTE. Intrinsic pathway activation will be assessed by measuring coagulation factor complexes with their natural inhibitor and by means of a factor XIa-dependent thrombin generation test, providing the most robust measurement of intrinsic coagulation pathway activation. Secondary objectives include evaluation and comparison of intrinsic pathway activation between cancer patients with VTE, cancer patients with no history of VTE, non-cancer patients with VTE a healthy individuals and evaluation of cancer-related activators of the intrinsic pathway, as well as evaluation of activation of the extrinsic pathway.

Study design

Investigator-initiated prospective multicenter cohort study

Study burden and risks

At baseline blood will be drawn from all patients for laboratory analysis (in total 22 ml). A telephone or clinic visit will be scheduled at day 30±10. All patients will be assessed for symptoms of (recurrent) VTE, bleeding, and (newly diagnosed) cancer. A second blood withdrawal will be performed in those patients who had VTE at baseline (both with and without cancer; in total 22 ml). There are no risks or benefits for patients given the observational nature of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients with active cancer and acute venous thromboembolism (VTE) in whom anticoagulant therapy is anticipated
2. Patients with active cancer and no suspicion or history of VTE
3. Patients with acute venous thromboembolism in whom anticoagulant therapy is anticipated, with no history of cancer or cancer treatment in the past 5 years and no suspicion of cancer at study entry.
4. Healthy volunteers
• No history of cancer or cancer-related therapy in the past 5 years.
• No history of VTE
• No suspicion of cancer or VTE at study entry
• No hospital admission in the past 6 months

Exclusion criteria

• Arterial thrombosis (ischemic stroke, myocardial infarction, peripheral arterial thrombosis) in the past six months
• Ongoing anticoagulant or antiplatelet therapy
• Mechanical heart valves
• Central venous catheters within 4 weeks prior to inclusion, or anticipated placement.
• One or more of the following risk factors for VTE:
- Known hereditary or acquired thrombophilia
- Viral or bacterial infection at time of inclusion
- Surgery, trauma or fracture of the leg within the previous 4 weeks
- Current known pregnancy
- Current estrogen therapy
• Inability for blood withdrawal at baseline

• Inability or refusal to provide written informed consent.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-10-2022
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	24-09-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL78061.018.21