PROTOCOL

TITLE:	Prediction of venous thrombosis during chemotherapy-the PINPOINT study
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1.0 SYNOPSIS

<table>
<tr><td>Study title:</td><td>PINPOINT: Prediction and prevention of Venous thrombo-embolism(VTE) during chemotherapy using serial determination of haemostasis biomarkers.</td></tr>
<tr><td>Objective</td><td>To serially determine plasma levels of haemostatic biomarkers (Thrombin generation, Factor VIIIc and Thrombomodulin) and compare their ability to predict VTE in cancer patients during chemotherapy compared with the Khorana score and the Vienna CAT nomogram.</td></tr>
<tr><td>Patient Population:</td><td>Inclusion criteria
Lung, ovarian, gastric, and pancreatic cancers undergoing a new course of chemotherapy.
Aged over 18
Exclusion criteria
Prior history of VTE
History of significant haemorrhage outside of surgical settings (previous 5 years)
Surgery less than 2 weeks prior to first baseline blood sample
Currently receiving anticoagulant therapy (excluding anti-platelet agents)
Currently on maintenance therapy (or had chemotherapy within 4 weeks of the first baseline sample)</td></tr>
<tr><td>Number of patients:</td><td>380</td></tr>
<tr><td>Duration of participation:</td><td>6 months</td></tr>
<tr><td>Primary Endpoint:</td><td>Objectively determined venous thromboembolism during chemotherapy</td></tr>
<tr><td>Study Design:</td><td>Prospective multicentre observational cohort study.
Blood samples collected at 4 time points:
Pre chemotherapy (T0)
4 weeks post baseline after one cycle of chemotherapy (T1)
12 weeks post baseline (T2)
at the end of current line of chemotherapy treatment (4-8 cycles (months) of chemotherapy) (T3)
Blood samples: 2 x 3-5 mls in Sodium Citrate tubes</td></tr>
<tr><td>Study schedule:</td><td><table><tr><th>Timepoints</th><th>Consent</th><th>Data collection</th><th>Blood sampling</th></tr><tr><td>Inclusion</td><td>X</td><td>X</td><td></td></tr><tr><td>Pre-chemotherapy (T0)</td><td></td><td>X</td><td>X</td></tr><tr><td>Month 1 (T1)</td><td></td><td>X</td><td>X</td></tr><tr><td>Month 3 (T2)</td><td></td><td>X</td><td>X</td></tr><tr><td>End of therapy (T3)</td><td></td><td>X</td><td>X</td></tr><tr><td></td><td></td><td></td><td></td></tr></table></td></tr>
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2. BACKGROUND AND RATIONALE

2.1 Background

Venous thromboembolism in cancer and chemotherapy

The association between malignancy and venous thromboembolism (VTE) is well documented with up to 20% of all cancer patients experiencing a VTE during their cancer journey[1]. VTE is a morbid, costly and potentially lethal complication of cancer and despite major advances in prophylaxis and treatment, VTE is the leading cause of death in cancer patients after the cancer itself[1]. The risk of VTE in cancer patients has increased over recent years in tandem with the rising rate of cancer worldwide and the increased survival of cancer patients [1].

Amongst solid tumours, pancreatic, lung, brain, stomach, and ovarian cancer are the most prothrombotic and are associated with high rates of VTE depending on tumour histology and treatment [2]. Prevention and treatment of cancer associated VTE represents an important medical challenge, since oncology patients concomitantly display higher rates of both bleeding and VTE recurrence than the non-cancer population [1,2]. This highlights the need for a careful risk/benefit assessment of anticoagulant prophylaxis. Recent guidelines recommend that, in ambulatory cancer patients receiving systemic therapy, at intermediate/high risk for VTE, thromboprophylaxis with Direct Oral Anti-Coagulants (DOACs) should be considered [3,4]. Classification of patients as being at low, intermediate, or high risk for VTE should be based on a validated risk assessment tool complemented by clinical judgment and experience.

The recommended tool for VTE risk assessment in cancer is the Khorana risk score [5], which was designed to identify ambulatory cancer patients at increased risk of VTE during chemotherapy using easily available clinical and laboratory variables prior to the commencement of therapy. However, the Khorana score performs poorly in cancers of a single type, especially cancers at high risk of VTE eg lung and ovary[6]. A validation study of >40,000 patients, showed that the guideline-recommended Khorana score was not effective in hepatobiliary, pancreatic, lung, or gynaecologic cancer[7]. In contrast, a recent report showed that biomarker-driven, risk directed primary thromboprophylaxis is effective in gastro-intestinal and lung cancers [8].

Factor VIIIc, Thrombomodulin(TM), Thrombin generation(TM modified) as biomarkers for VTE

The biology of chemotherapy associated VTE is complex. Exposure of vascular endothelial cells to common chemotherapeutic agents can alter anticoagulant activity with the loss of a thromboresistant phenotype[9,10]. Binding of thrombin to thrombomodulin (TM) on the endothelial cell surface leads to the activation of protein C(aPC), a major regulatory pathway in coagulation, which is accelerated by the endothelial protein C receptor(EPCR)[11]. aPC can inactivate both FVIII and FV resulting in a downregulation of thrombin and fibrin production. Data has shown that the aPC pathway is dysregulated during chemotherapy, resulting in a reduction in the inhibitory effects of aPC[10].

Failure of protein C activation or resistance to the inhibitory effects of aPC(both genetic and acquired) is a common cause of VTE in the non cancer population[11]. Factor VIIIc(FVIIIc) has been shown to be predictive of VTE in cancer patients with highest levels of FVIIIc in patients who developed VTE following chemotherapy compared with matched controls [12,13]. Factor VIIIc is predictive of VTE in a variety of clinical settings, even after adjustment for inflammatory markers [23]

Preliminary studies have shown that plasma levels of soluble TM are reduced *in vivo* in patients who develop VTE following chemotherapy suggesting that TM is an important mediator of chemotherapy associated VTE and was inversely correlated with thrombin generation [12]. The thrombin

generation assay is associated with increased risk of VTE in cancer patients and sensitivity of the assay can be increased by addition of TM. Preliminary data suggests that the TM modified thrombin generation assay (TGA-TM) is increased in patients who develop VTE following chemotherapy [12]. This data suggests that soluble TM, TGA-TM and FVIIIc levels measured serially may be effective alone or in combination as dynamic predictive biomarkers for VTE during chemotherapy.

2.2 Rationale

Previous studies have used a variety of biomarkers to predict VTE in cancer patients, however prediction was based on one sample and does not account for the dynamic nature of thrombogenesis particularly during chemotherapy, when the progressive effects of endothelial damage, material from dying tumour cells and an inflammatory response may combine to produce VTE[12]. The interplay between cancer, coagulation activation and chemotherapy is a dynamic process, unlikely to be represented by a single risk assessment at the start of therapy. Dynamic risk assessment using serial measurement of biomarkers during therapy has been recommended as a more effective approach to risk assessment [14,4]. The most recent ESMO guidelines have suggested repeated risk assessment using the new Vienna CAT score (a nomogram based on D-dimer levels and tumour site) may improve risk prediction [4] however this has not been tested and the specificity of D-dimer as a biomarker for VTE in this setting is low [15]. Recent validation studies of a single measurement of the Vienna- CAT nomogram showed only a modest improvement in discriminatory ability compared with the Khorana score [16]. VTE risk is exacerbated by chemotherapy and hence biomarkers which capture the effects of chemotherapy on thrombus formation are more likely to be reflective of chemotherapy associated VTE.

2.3 Hypothesis

Serial determinations of TGA-TM, FVIIIc and TM will predict VTE in ovarian, pancreatic, lung and gastric cancer patients undergoing chemotherapy more effectively that the guideline recommended Khorana score or serial determinations of the Vienna CATS score.

2.4 Planned analysis

Lung, ovarian, gastric and pancreatic cancer patients (n=380) who are scheduled to undergo chemotherapy will be recruited from three large centres for cancer treatment in Ireland (Trinity St. James Cancer Institute, Cork University Hospital, Mater Hospital). The primary endpoint for the study will be objectively diagnosed VTE which occurs during chemotherapy. Following full and informed written consent, venous blood samples will be obtained pre-treatment, after month 1, 3 and at the end of treatment (or prior to interval cytoreductive surgery in the case of neoadjuvant patients). Plasma levels of TGA-TM, sTM, FVIIIc and D-dimer will be measured at each time point. All biomarker analysis will take place in the Coagulation Research Laboratory, Dept of Gynaecology, Trinity St. James Cancer Institute. The Khorana score will be calculated at the start of therapy in each patient. The Vienna CAT score will be calculated at each time point using the D-dimer values obtained. Serial levels of each biomarker in patients who develop VTE will be compared with those who remain thrombosis free. The predictive ability of each biomarker (alone and in combination) will be compared with (1) the current recommended risk assessment model (Khorana score) performed prior to treatment and (2) serial determinations of the Vienna CAT nomogram at each timepoint.

3.0 OBJECTIVE OF THE STUDY

The aim of the study is to serially measure TGA-TM, sTM, and FVIIIc levels in lung, ovarian, pancreatic, and gastric cancer patients during chemotherapy and compare their ability to predict VTE with the Khorana score and serial determinations of the new Vienna CAT score.

4.0 STUDY ENDPOINT

Objectively diagnosed VTE occurring during chemotherapy

5.0 PATIENT POPULATION

All patients with a diagnosis of ovarian, lung, gastric or pancreatic cancer who are scheduled to undergo a course of chemotherapy are eligible for the study.

5.1 Patient Selection Criteria

5.1.1 Inclusion criteria

- Patients with a diagnosis of ovarian, lung, gastric or pancreatic cancer who are scheduled to undergo a course of chemotherapy who:

  are undergoing adjuvant or neoadjuvant chemotherapy
  or
  who are undergoing chemotherapy for relapsed disease
  or
  Patients who are undergoing targeted therapy in combination with chemotherapy

- Patients who are over 18 years of age
- Patients who are able to give full and informed written consent

5.1.2 Exclusion criteria

- Prior history of a documented VTE event within the last 5 years (excluding central line associated events whereby patients completed anticoagulation > 3 months previously)
- Any history of significant haemorrhage (requiring hospitalization or transfusion) outside of a surgical setting within the last 5 years
- Familial bleeding diathesis
- Known diagnosis of disseminated intravascular coagulation
- Surgery within 2 weeks of first baseline sample (with the exception of porth-a-cath implantation or biopsy)
- Chemotherapy or immunotherapy 4 weeks before first baseline sample
- Currently receiving long term anticoagulant therapy (Low Molecular Weight Heparin(LMWH), Direct Oral Anticoagulants(DOACs), Warfarin). Patients receiving aspirin, ticlopidine, clopidogrel or LMWH at a thrombo-prophylactic dosage for a short period (ie post cancer surgery or during short hospital stay) will be included provided they have completed thromboprophylaxis therapy at the first blood sampling time point.

5.2 Recruitment and consent

Eligible patients receiving treatment at each of the study centres (St. James Hospital, Mater Hospital and Cork University hospital) will be invited to participate by a member of the investigator team. Patients will be provided with the study information (patient information leaflet and consent form) and will give full written consent in person if participating in the study.

5.3 Number of patients

The accrual target is 380 patients.

5.4 Anticipated enrolment period and study completion date

The anticipated enrolment period is 36 months. The study enrolment will be completed in 2028. The final sample and data collection will be June 2029

5.5 Duration of patient participation

Patients will participate from the date of enrolment until completion of the current line of treatment (4-6 cycles of chemotherapy), occurrence of a VTE, or 6 months from enrolment as appropriate.

5.6 Patient and study discontinuation criteria

Patients are free to withdraw from the study at any time upon request.

Additional reasons for withdrawal

- Study completion
- Long term anticoagulation (prophylaxis or treatment)
- Lost to follow-up
- Discontinuation of chemotherapy
- Death
- Other
- Investigator decision

6. STUDY DESIGN

6.1 Type of study design

Multicentre prospective observational cohort study

6.2 Timing of sample and data collection

6.2.1. Blood Sample collection

Venous blood samples (1 x 5ml Na Citrate) will be taken into 3.13% sodium citrate (1:9) tubes with the minimum venous stasis at the time of routine pre-chemotherapy blood draws. Blood samples will be taken before the first cycle(T0), second cycle (T1), after the third cycle (T2) of chemotherapy. The final sample will be following 4-6 cycles of chemotherapy or at the end of the current line of treatment (T3). All samples will be taken to coincide with the patient's routine blood samples. For patients on weekly chemotherapy, T1 will be taken after 3-4 weeks, T2 at 10-12 weeks, T3 at the end of current weekly treatment.

Timepoints	Consent	Data collection	Blood sampling
Inclusion	X	X	
Pre-chemotherapy (T0)		X	X
Month 1 (T1)		X	X
Month 3 (T2)		X	X
End of therapy (T3)		X	X

6.2.2 Sample processing

Samples will be centrifuged at 2000 g for 20 minutes at 4°c in the processing laboratory in each centre. The resulting platelet poor plasma will be carefully removed and aliquoted into 5 x 500µl aliquots in labelled microtubes. All tubes will be labelled with the patient study number and the date. Aliquots will be snap frozen and stored at -80°c. All samples should be processed and stored within 2 hours of phlebotomy. Samples will be stored at each centre and transferred in batches to the Coagulation Research Laboratory, Dept of Obstetrics and Gynaecology. Trinity St. James Cancer Institute for analysis. All sample transport costs will be covered by the Coagulation Research laboratory.

6.2.3 Data collection

The study data will be collected using REDCAP(https://www.project-redcap.org/). Study data will be entered by authorised site personnel into the electronic data capture system.

The following data will be collected for each patient.

Inclusion/baseline (T0)

- Age
- Weight
- Sex
- BMI
- Consent yes/no
- Inclusion/exclusion criteria
- Date of diagnosis
- Tumour site
- Tumour histology
- Stage of cancer
- Grade of cancer
- Relevant past Medical history (Diabetes Mellitus, Hypertension,Chronic liver or kidney disease, Chronic respiratory disease, heart disease, cancer, auto-immune disease, neurological disease)
- ECOG status
- Relevant current medication- Aspirin, Clopidogrel, Dipyridamole, Ticagrelor, Ticlopidine.
- Date of surgery (if applicable)
- Previous chemotherapy
- Haemoglobin (on day of T0 blood sampling)
- White cell count
- Neutrophils
- Lymphocytes
- Platelets

Follow up blood sampling visits. T1-T3

- Chemotherapy treatment details
- Number of cycles completed
- New/discontinued relevant medication
- New diagnosis of relevant conditions (see list at baseline visit) since last visit-

- VTE since baseline: Yes/No
  If yes:
  - Date of VTE diagnosis (date of CTPA, VUS as appropriate)
  - VTE details- PE. DVT etc

- Hospital admissions since last visit
  - Date of admission
  - Duration of hospital stay
  - Reason for admission
  - VTE prophylaxis during admission

- Laboratory values (most recent result)
  - Haemoglobin
  - White cell count
  - Neutrophils
  - Lymphocytes
  - Platelets

6.3 Laboratory Biomarker analysis:

All biomarker analysis will take place at the Coagulation Research Laboratory, Dept of Obstetrics and Gynaecology, Trinity St. James Cancer Institute, St. James's Hospital.

6.3.1 Laboratory methods

sTM will be measured using Enzyme Linked Immunosorbent Assay (ELISA) (R&D systems) and FVIIIc will be measured using commercially available chromogenic substrate assay (Hyphen Biomed France). TGA-TM will be measured using commercially available reagents (Stago) as previously described [10]. D-dimer will be measured using a 2-step procedure (VidasTM D-dimer Exclusion II, Biomerieux, France).

6.3.2 Calculation of the Khorana risk score(KRS) and the Vienna CAT score

BMI data and complete blood cell count values will be recorded at enrolment prior to the start of chemotherapy. and the KRS calculated as previously described [5]. Lung and ovarian cancer patients are assigned 1 point for tumour site category, gastric and pancreatic cancers are assigned 2 points. The Vienna CAT nomogram will be calculated according to the published formula [17] at each sampling point in the study. Calculation of the Vienna CAT score and the KRS will be performed by the biomarker laboratory from the collected data.

7.0 STATISTICAL CONSIDERATIONS

7.1 Analysis

Statistical analysis of the primary outcome data will be performed by Dr. Lucy Norris in collaboration with Prof. Pilib O'Broin, School of Mathematical & Statistical Sciences, University of Galway.

7.2 Sample size calculation

Power calculations will be based on previous data [12]. sTM FVIIIc, TGA-TM effect sizes and standard deviations of the outcome variable were 92.1(154), 1050 (1441), 34 (45.96) respectively. Type I error is set at 0.01 to allow for the effect of multiple time points and type II.error = 0.2. A minimum of 31 patients in the VTE group will be required. Given a predicted incidence of VTE of 10-20%, this

requires a sample size of 310 patients to complete the study at a 10% VTE incidence rate. Allowing for dropouts, 380 patients will be recruited to the study. Sample sizes for regression analysis are estimated using a rule of thumb of 10 individuals expected to experience the event (VTE) for each predictor in the model. In this instance, with an expected 10-20% incidence of VTE, if 30-60 individuals experience VTE, this will allow 3-6 predictors to be fitted to the model.

7.2 Statistical analysis of the data

Analysis will be performed when the required data has been received following completion of patient enrolment and all biomarker analysis is complete. Data will be assessed for normal distribution and log transformed where normal distribution criteria are not met. Biomarker data will be reported as continuous data and will be reported as median (25-75th centile). Potential confounders will first be identified using univariate analysis of clinical risk factors to identify differences between VTE cases and controls. These covariates will then be incorporated into the model.
The JMBayes2 R package from the Rizopoulos group (https://drizopoulos.github.io/JMbayes2/) will be used to fit a joint model using a Markov chain Monte Carlo (MCMC) approach. The first sub-model, a multivariable linear mixed model will be used to model longitudinal changes in the three biomarkers; the second sub-model, a competing risks model, will be used to model the time-to-event data. Using this approach, the first sub-model will account for the non-independence of repeated measures from the same patient while allowing for missing longitudinal data, while the second sub-model will also allow for the inclusion of clinically relevant covariates such as treatment type, tumour site etc. The resulting associations will be compared with current models (Vienna CATS score) to identify which biomarker or biomarker(s)have the strongest association with VTE. Sensitivity, specificity, NPV, PPV of the biomarker(s) above/below a cutoff will also be compared with the Khorana score and the Vienna CATS score. Statistical analysis of pseudonymised data will take place in the Dept of Mathematics, University of Galway (Prof Pilib O'Broin).

8.0 ADMINISTRATIVE RESPONSIBILITIES

8.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The investigator will be thoroughly familiar with the study requirements as outlined in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

8.2 Ethical considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (current edition located at: http://www.wma.net/en/30publications/10policies/b3/).
An ethics committee at each centre will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The protocol, informed consent, written information given to the patients, annual progress reports and any revisions to these documents will be provided to them by the sponsor. The study will only be conducted at sites where their full approval has been obtained. Explicit consent will be obtained through the consent form. Participation or non-participation in the study will not affect the patient's medical treatment in the hospital.

8.3 Data Protection

A data protection impact assessment (DPIA) will be conducted and reviewed by the Trinity College Data Protection Officer (DPO) and the DPO in each participating hospital.

Published guidelines to be followed:

- Human Rights Privacy and Confidentiality
- TCD Good Research Practice Policy

Data Protection Legislation such as the Data Protection Acts 1988 to-2018 will be complied with.

The legal basis for processing personal data in the study is under Article 6(1)(e) and Article 9(2)(j) - research in the public interest. Explicit consent will also be given as a safeguard under the Health Research Regulations -2018 (-As amended)

Pseudonymised study data will be held securely on site in the Trinity St. James Cancer Institute, St James's Hospital. Patient consent forms will be retained for 7 years on site at each centre.

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