STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN (SUMMARY)

Official Title: Thromboembolic Risk screening in patients with cancer and SARS-Cov-2 Infection

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1. Study Objective : Since December 2019, outbreak of COVID-19 caused by a novel virus SARS-Cov-2 has spread rapidly around the world and became a pandemic issue. First data report high mortality in severe patients with 30% death rate at 28 days [Tang N, 2020]. Exact proportions of the reasons of death are unclear: severe respiratory distress syndrome is mainly reported which can be related to massive cell destruction by the virus, bacterial surinfection, cardiomyopathy or pulmonary embolism [Danzi GB *et al*, 2020]. The exact proportion of all these causes is unknown and venous thromboembolism could be a major cause because of the massive inflammation reported during COVID-19 [Huang C *et al*, 2020].
High levels of D-dimers and fibrin degradation products are associated with increased risk of mortality and some authors suggest a possible occurrence of venous thromboembolism (VTE) during COVID-19 [Driggin E *et al*, 2020].
Indeed, COVID-19 infected patients are likely at increased risk of VTE. In a multicenter retrospective cohort study from China, elevated D-dimers levels (>1g/L) were strongly associated with in-hospital death, even after multivariable adjustment.
Also, interestingly, Tang *et al* (2020) found that the prophylactic administration of anticoagulant treatment was associated with decreased mortality in a cohort of 449 patients, with a positive effect in patients with coagulopathy (sepsis-induced coagulopathy score ≥ 4) reducing the 28 days mortality rate (32.8% versus 52.4%, p=0.01).
However the presence/prevalence of VTE disease is unknown in COVID-19 cancer patients with either mild or severe disease. Cancer patients are at a higher risk of VTE than general population (x6 times [Donnellan *et al*, 2017]) and could be consequently at a further higher of VTE during COVID-19, in comparison with non-cancer patients.
The exact rate of VTE and pulmonary embolism during COVID-19 was never evaluated, especially in cancer patients, and is of importance in order to understand if this disease needs appropriate prophylaxis against VTE.
The largest series of cancer patients so far included 28 COVID-19 infected cancer patients: the rate of mortality was 28.6%. 78.6% of them needed oxygen therapy, 35.7% of them mechanical ventilation. Pulmonary embolism was suspected in some patients but not investigated due to the severity of the disease and renal insufficiency, reflecting the lack of data in this situation [Zhang L *et al*, 2020].
The aim of the present study is to analyze the rate of symptomatic/occult VTE in a cohort of patients with cancer.

<u>Expected benefits</u>
Anticipated benefits of the research are the detection of VTE in order to treat it for the included patient.
For all COVID-19 positive cancer patients it will enable to provide some guidelines and determine which patient are at risk for VTE and which will need ultrasound to detect occult VTE.

<u>Foreseeable risks</u>
Foreseeable risks for patients are non-significant because the additional procedures needed are ultrasound exam, and blood sample test.

2. Study Design & Population : Retrospective and prospective (ambispective), multicentric study to evaluate the occurrence of venous thromboembolism during COVID-19 infection.
Indeed, because the outbreak can end within the next 3-6 months, we may not be able to answer the question if we only focus on patients investigated prospectively. We then decided to include patients from medical team who are already systemically screening patients with COVID-19 disease for VTE.
For control cohort patients, in case of positive test at reevaluation, patient will switch to the infected cohort arm and restart the follow up for 42 days.

3. Eligibility Criteria

For the prospective cohort:

Inclusion criteria

To be eligible for participation in this trial, the subject should fulfill the following criteria:

1. COVID-19 testing;
2. Age ≥ 18-years old;
3. Patient treated for histologically proven cancer (under treatment or last anti-neoplastic treatment < 3 months);
4. Patient willing and able to provide written informed consent/assent for the trial;
5. Patient affiliated with a health insurance system.

Exclusion criteria

The subject should not enter into the study if any of the following criteria are fulfilled:

1. Patient not able to give free consent;
2. Patient not able to understand the protocol;
3. Patients under 18 years;
4. Vulnerable persons as defined by article L1121-5 - 8:
    a. Pregnant women, women in labour or breast-feeding mothers, persons deprived of their freedom by judicial or administrative decision, persons hospitalized without their consent by virtue of articles L. 3212-1 and L. 3213-1 and who are not subject to the provisions of article L. 1121-8
    b. Persons admitted to a social or health facility for reasons other than research
    c. Adults subject to a legal protection order or unable to give their consent.

For the retrospective cohort:

Only patients coming from medical teams who are screening systematically VTE will be included (Centre Antoine Lacassagne, CHU of Nice, Centre Hospitalier Princesse-Grâce Monaco, Clinique Saint-George Nice).

Inclusion criteria:

To be eligible for participation in this trial, the subject should fulfill the following criteria:

1. COVID-19 testing ;
2. Age ≥ 18 years old ;
3. Patient treated for histologically proven cancer (under treatment or last anti-neoplastic treatment < 3 months at the time of COVID-19 testing);
4. For the infected cohort: patient being screened for VTE at least one time 7 weeks after the COVID-19 diagnosis;

5. Complete blood count available at time of COVID-19 testing (+/-14 days) to be able to calculate the Khorana score;
6. Patient informed and not opposed to the data processing;
7. Patient affiliated with a health insurance system.

Exclusion criteria:

The subject should not enter into the study if any of the following criteria are fulfilled:

1. Patient not able to give free consent;
2. Patient not able to understand the protocol;
3. For the infected patients: VTE screening not performed;
4. No available complete blood count at time of COVID-19 testing;
5. Medical file and clinical follow-up not available during the study period (7 weeks after the COVID-19 test);
6. Patients under 18 years;
7. Vulnerable persons as defined by article L1121-5-8:
   a. Pregnant women, women in labour or breast-feeding mothers, persons deprived of their freedom by judicial or administrative decision, persons hospitalized without their consent by virtue of articles L. 3212-1 and L. 3213-1 and who are not subject to the provisions of article L. 1121-8
   b. Persons admitted to a social or health facility for reasons other than research
   c. Adults subject to a legal protection order or unable to give their consent

4. Statistical Analysis Plan (SAP)

Primary Outcomes: To evaluate the rate of venous thromboembolism at 42 days during COVID-19 infection in cancer patients.

- **Analysis:** Descriptive statistics were used to calculate percentages and 95% Confidence Intervals (CI).
- **Safety:** All-cause mortality was tracked descriptively. No formal sample size calculation or complex sequential modeling was required for this observational study.