Cancer-Associated Thrombosis

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Background

Cancer-associated thrombosis (CAT) is one of the leading causes of morbidity and mortality for cancer patients. CAT commonly occurs in patients with clinically active malignancy; however, there is a subset of patients where thrombosis can be the first manifestation of their cancer. The correlation between malignancy and thrombosis has been reported as early as 1823. Patients with malignancy often experience increased risk of thrombosis, both venous and arterial. Clinical VTE remains one of the most common causes of mortality and morbidity among cancer patients. Pathophysiology of this disease stems from the hypercoagulable state related to the increasing production of substances like tissue factor that have high procoagulant activity. The thromboembolic disease can be the first manifestation of occult malignancy or more commonly occur within six months of a cancer diagnosis. We have reviewed the current literature on CAT.

Contributing Factors

Multiple factors contribute to the increased risk of arterial and venous thromboembolism in cancer patients:

1. The tumor's tissue and anatomical factors
2. Patient's comorbidities including obesity and advanced age
3. Surgical and medical oncological treatment

The rates of VTE are higher in cancer when compared to non-cancer patients (Fig.1).

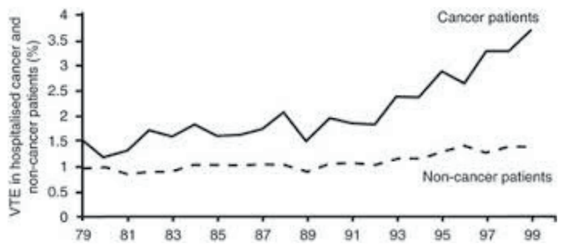

Figure 1: Rates of VTE in cancer when compared to non-cancer patients.

VTE Risk in Cancer Patients

Multiple published accounts show an increased risk of VTE in patients with malignancy with prevalence as high as 20%. A large case-control study in the Netherlands examined 3220 patients aged 18 to 70; the study found the overall risk of venous thrombosis to be 7-fold higher in patients with malignancy, the highest risk was in the first few months after diagnosis with the highest risk increase seen in patients with hematological malignancies, lung cancer, gastrointestinal cancer, or with distant metastases. In another case-control study in Minnesota, a 4-fold increased risk of VTE was found in patients with cancer, while patients receiving chemotherapy experienced an even higher risk. Cancer patients also face an increased risk of arterial thromboembolism. In a large retrospective study with 279,719 pairs of cancer patients and matched controls, the 6-month incidence of myocardial infarction was 2.0% in cancer patients compared to 0.7% in control patients, while for ischemic stroke, the incidence was 3.0% for cancer patients compared to 1.6% for control patients. The study also found that cancer patients experiencing arterial thromboembolism had a poor prognosis, with a 3-fold increased hazard for death.

Mechanism of CAT

Tissue factor produced by malignant cells appears to trigger the coagulation cascade leading to the formation of Factor Xa, while some cancer cells can produce cancer procoagulant that acts directly on Factor Xa.
In addition to the potential procoagulant effect of cancer cells, anti-cancer therapy has shown to be an additional cause of cancer-associated thrombosis. Different chemotherapeutic agents, including methotrexate, cyclophosphamide, cisplatin, doxorubicin, 5-fluorouracil, and lenalidomide, have been found to increase the risk of VTE and mortality significantly. Other causes include venous stasis due to compression of blood vessels by tumor or prolonged immobility in critically ill cancer patients.

Organs affected by CAT

Several organs can be affected by CAT that cause VTE (Figure 2). The most affected organ is pancreas, followed by mesothelioma, lung brian, etc.

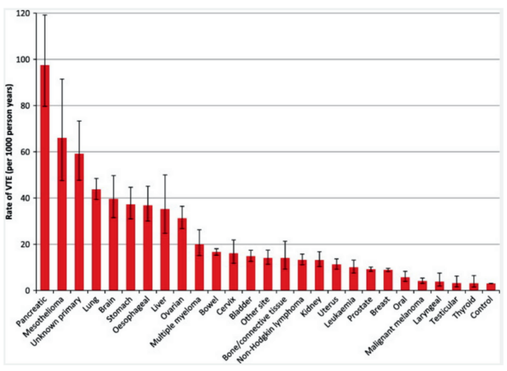

Figure 2: Rates of VTE caused by various types of cancer

Mortality Rates of CAT

- CAT diagnosis oftentimes leads to an earlier, untimely death.
- Some studies report the survival rate post-diagnosis to be as low as 6.3 months, but survival can be anywhere from 13-16 months post-diagnosis

Cellular Indices of CAT (Fig. 3)

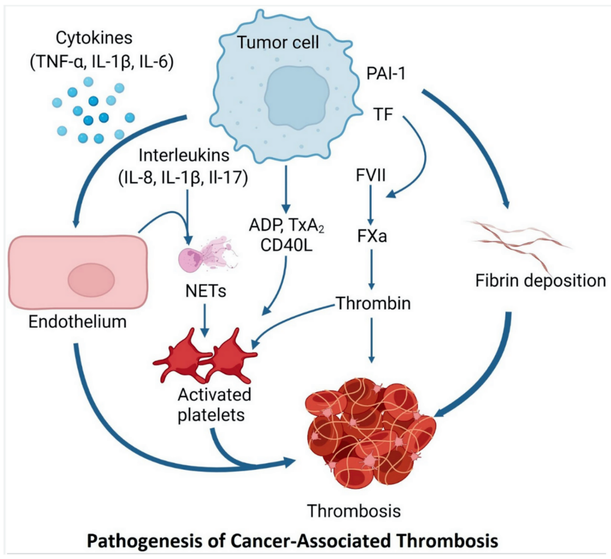

Figure 3: Cellular indices of CAT

Diagnosis of CAT

1. History and physical. Thromboembolic events can either occur in patients with a known history of malignancy or can be the first manifestation.
2. Patients can present with venous thromboembolism as deep venous thrombosis or pulmonary embolism and less likely as arterial thromboembolism with ischemic stroke and myocardial infarction.

Differntial Diagnosis

The following conditions must be ruled out when making a diagnosis of CAT:
1. Thrombophilic disorders
2. Nephrotic syndrome
3. Antiphospholipid syndrome
4. Severe liver disease
5. Inflammatory bowel disease

Prognosis

- CAT increases mortality in cancer patients.
- In a review of 8 million Medicare patients admitted for VTE, the probability of death within six months of admission for cancer patients was 94% compared to 29% with non-cancer patients.
- The majority of deaths in patients with cancer-associated thrombosis were related to arterial thrombosis (myocardial infarction, ischemic stroke) rather than VTE.
- In a review of 4466 ambulatory patients, thromboembolic disease accounted for 9.2% of deaths. 5.6% were related to arterial thrombosis

Management of CAT

- Given the increased risk of thromboembolism, patients with clinically active malignancy would benefit from thromboprophylaxis.
- A meta-analysis looking at a total of 33 trials and 11,972 patients provided more evidence that thromboprophylaxis decreased the incidence of VTE in cancer patients who were undergoing chemotherapy or surgery, while no apparent increase in the incidence of significant bleeding.
- Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend anticoagulation with unfractionated heparin or low molecular weight heparin in hospitalized cancer patients as thromboprophylaxis.
- Mechanical prophylaxis should be used instead of anticoagulation therapy in patients experiencing active bleeding, thrombocytopenia (platelet count below 50,000/mcL), evidence of hemorrhagic coagulopathy, or have an indwelling neuraxial catheter.
- Contraindications to the use of mechanical prophylaxis include acute deep venous thrombosis and severe arterial insufficiency.
- Surgical pelvic or abdominal oncology patients would benefit from continuing VTE prophylaxis up to four weeks post-operation.
- The use of aspirin or anticoagulation therapy for patients with multiple myeloma on immunomodulatory medications is recommended based on risk stratification with the IMPEDE VTE score.
- For patients with solid cancers on chemotherapy and high Khorana score, prophylactic anticoagulation with direct oral anticoagulation or low molecular weight heparin showed a decrease in the incidence of pulmonary embolism.

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- In patients with DVT located in inferior vena cava, iliac, femoral, and popliteal veins placement of retrievable vena cava filters can prevent pulmonary embolism.
- In patients with superficial venous thrombosis, if it is related to peripheral catheter, current guidelines recommend removing the catheter and consider anticoagulation if thrombus progression occurs.
- In patients with superficial venous thrombosis non-catheter related especially in lower extremities, recommendations are for at least six weeks of anticoagulation.

Recommendations by ASH

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Center with international collaborators.

RECOMMENDATION 1. For hospitalized medical patients with cancer without VTE, the American Society of Hematology (ASH) guideline panel suggests using thromboprophylaxis over no thromboprophylaxis.
RECOMMENDATION 2. For hospitalized medical patients with cancer without VTE, in which pharmacological thromboprophylaxis is used, the ASH guideline panel suggests using LMWH over UFH
RECOMMENDATION 3. For hospitalized medical patients with cancer without VTE, the ASH guideline panel suggests using pharmaco- logical thromboprophylaxis over mechanical thromboprophylaxis
RECOMMENDATION 4. For hospitalized medical patients with cancer without VTE, the ASH guideline panel suggests using pharmacological thromboprophylaxis over a combination of pharmacological and mechanical thromboprophylaxis.

Patient Education

- Patients with active malignancy are at risk of developing venous and arterial thromboembolism.
- It is important to educate patients on their increased risk of developing cancer-associated thrombosis and possible presenting symptoms, including unilateral leg swelling, palpitations, chest pain, dyspnea, and stroke.
- For non-cancer patients with unprovoked venous thromboembolism, it is crucial to perform age-appropriate cancer screening to evaluate for hidden malignancy.

Conclusion

CAT is one of the leading causes of morbidity and mortality. Factors contributing to CAT are obesity, old age. The rates of VTE are higher in cancer vs non-cancer patients. Common organs affected are pancreas, lung, and brain. Treatment of CAT includes thromboprophylaxis, mechanical prophylaxis, LMWH, and DOACs.

References

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TRIM LINE
SAFE ZONE
12998627_20473430 40 x 56
Front 40 x 56 trim size