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Spot the CLOT: Treatment considerations for CAT

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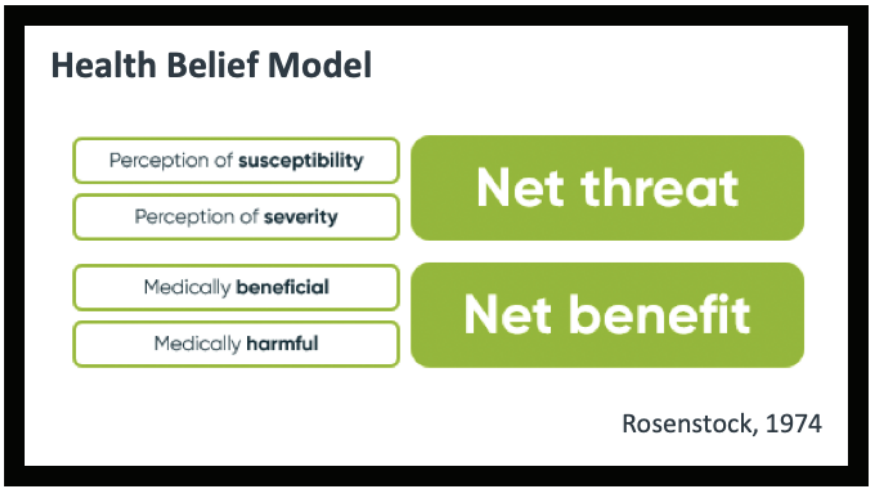
This is the fourth and final article in the Spot the CLOT series. To date, we have addressed the significance of venous thromboembolism (VTE) in patients with cancer, knowledge deficits about cancer-associated thrombosis (CAT) in both cancer patients and providers, and opportunity for addressing these knowledge gaps. This article will focus on a practical treatment approach, supported by a theoretical framework. In addition, we will discuss idiopathic VTE, often the first clue of a yet to be discovered cancer.



THEORETICAL FRAMEWORK

The Health Belief Model (HBM) is a framework used to motivate persons to take action that has positive health benefits and avoids negative health consequences. HBM advocates that patient behaviours are influenced by their perception of susceptibility to an illness, the severity of the illness, the benefits of taking action, and the barriers to that action (Rosenstock, 1974). HBM theory can be used as a framework to guide treatment plans including patient education and anticoagulant treatment in an effort to increase adherence.

The importance of patient education has been described in an earlier Spot the CLOT series entitled, 'What cancer patients want to know' (Bayadinova et al., 2022). The HBM highlights the importance of educating cancer patients on their risk of VTE, common signs and symptoms, and its impact on quality of life. These topics signify the 'net threat' and help patients and their family members understand why CAT is a concern.

The anticoagulation treatment plan, including drug choice and duration of therapy, comprises the 'net benefit' of CAT treatment. Patient understanding and appreciation of anticoagulant therapy is important to optimize adherence to treatment plans.

CAT ALGORITHM

A simple algorithm is available for the treatment of CAT (Carrier et al., 2021). The algorithm was originally developed in 2018, and refined in 2021 with recognition of drug-drug interactions, patient and provider preferences, and to include upper extremity DVT (Figure 1).

Use of the CAT algorithm helps target the right anticoagulant for the right patient with consideration for evidence-based practice based on the latest CAT studies including CLOT, CATCH, Hokusai VTE Cancer, SELECT-D, and CARAVAGGIO trials.

The algorithm first identifies patients with CAT without contraindication to anticoagulation. Next, it stratifies patients into high and low bleeding risk; for CAT patients with a high bleed risk, a low molecular weight heparin (LMWH) treatment strategy is recommended. The LMWH strategy offers superior or equal efficacy while maintaining safety in the high bleed risk patient.

For those with low bleeding risk, the algorithm further stratifies by cancer type, then for significant drug-drug interactions. Patients with significant drug-drug interactions should be managed with LMWH for the CAT treatment. Patients with unresected intraluminal gastrointestinal or genitourinary cancers should also be managed with LMWH therapy given their propensity for bleeding. The use of LMWH offers the flexibility of dose reduction should there be concerns for thrombocytopenia, bleeding, or a need for temporary interruption of anticoagulation. Injection technique is an important component of the treatment plan. Instructions for injection technique can be found on the Thrombosis Canada website (https://thrombosiscanada.ca/wp-content/uploads/2016/10/M159-LMWH_Oct2016.pdf and https://

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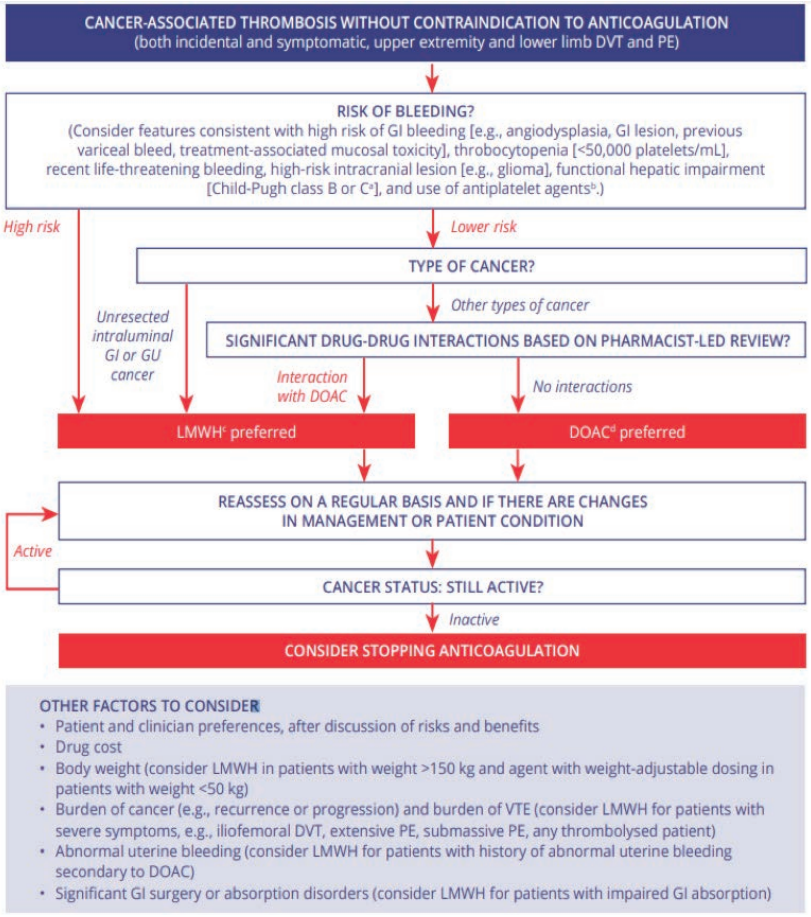
Figure 1

The CAT Algorithm (adapted from Carrier et al., 2021)



[a] None of the DOACs are recommended for use in patients meeting criteria for Child-Pugh class C, with use or rivaroxaban being contraindicated in patients with hepatic disease (including Child-Pugh class B and C) associated with coagulopathy and having clinically relevant bleeding risk. Apixaban should be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh class A or B), while these patients exhibited comparable pharmacokinetics and pharmacodynamics to healthy controls when treated with edoxaban; [b] Use of antiplatelet agents should be assessed, and discontinuation should be considered in the absence of a strong indication. Shared decision-making with other healthcare providers is warranted. [c] Currently, dalteparin, enoxaparin, and tinzaparin have randomized controlled trial evidence in cancer-associated thrombosis, with the evidence base being stronger for dalteparin and tinzaparin. Refer to the relevant product monograph for appropriate dosing. [d] Currently, apixaban, edoxaban, and rivaroxaban have randomized controller trial evidence in cancer-associated thrombosis, with stronger evidence for apixaban and edoxaban. Refer to relevant product monograph for appropriate dosing. Source: https://thrombosiscanada.ca/cat-treatment-algorithm-2021/
DVT = deep vein thrombosis; PE = pulmonary embolism; GI = gastrointestinal; GU = genitourinary; DOAC = direct-acting oral anticoagulant; LMWH = low molecular weight heparin; VTE = venous thromboembolism

thrombosiscanada.ca/wp-content/uploads/2016/10/M159-LMWH_French_Oct2016.pdf) including useful patient handouts and an instructional video for patients to view (https://www.youtube.com/embed/9ZePmmlfaAk) .

Patients with low risk of bleeding and most other cancer types may be managed with direct oral anticoagulants (DOACs). DOACs offer an oral anticoagulation alternative and are once or twice daily dependent on anticoagulant choice. DOACs have a short half-life (~8-14 hours) and are dependent on kidney function. Apixaban/Eliquis is the least dependent on renal function. Certain DOACs are best absorbed with food (rivaroxaban/Xarelto) and therefore should be avoided in patients with nausea, poor nutritional intake, or surgeries potentially affecting absorption (e.g., gastrectomy).

Patients should be reassessed on a regular basis with consideration for cancer status, bleeding risk, possibility of dose reduction and, importantly, patient preference. Cancer patients need to understand the association between cancer and thrombosis. The Thrombosis Canada website offers a handout available for download for CAT patients, and perhaps more importantly for cancer patients without thrombosis, so they may be aware of this potentially fatal complication of cancer.

COMPLICATIONS

Awareness of potential treatment complications is important in a patient with CAT. Although treatment for VTE is often successful in the general population, a cancer diagnosis adds a layer of complexities. Complications may be more common in patients with cancer due to high-risk cancers, cancer- and treatment-related alterations in chemistry and hematology. These complication may include bleeding, thrombocytopenia, or treatment failure in the form of thrombosis extension or recurrence.

Bleeding

The most common complication associated with anticoagulant therapy is bleeding with a reported 6-fold increased risk in patients with CAT (Schulman et al., 2015). Major bleeding is defined as a drop in hemoglobin of 20 g/L or more or a need for transfusion of at least two units of packed red blood cells. In the general population, most episodes of major bleeding occur shortly after initiation of anticoagulant treatment with the absolute risk in the first three months of treatment approximately 2%, decreasing to 1% over a cumulative treatment period of six months (Klok et al., 2015). Risk in patients with CAT is significantly higher with a risk of 7% in the first three months of treatment, increasing to 9.3% in a six-month treatment period (Klok et al., 2015). A separate study reported 4.9% of patients without cancer developing major bleeding in 12 months of anticoagulant treatment, compared to 12.4% of cancer patients, a 2.5-fold

increase (Prandoni et al., 2002). Of note, patients with less extensive cancer had similar bleeding rates to the non-cancer population (Prandoni et al., 2002). Importantly, moderate burden of cancer increased the risk two- to three-fold, and in patients with advanced cancer, this was increased five-fold (Prandoni et al., 2002).

The increased risk was often associated with bleeding at the site of cancer (Prandoni et al., 2002). Other patient characteristics associated with an increased risk of bleeding included older age, female sex, previous bleeding events, and uncontrolled hypertension, as well as renal and liver insufficiency (Klok et al., 2015). Major bleeding is typically managed with a temporary interruption of anticoagulation, supportive measures, and identification and definitive treatment of the bleed if possible. A decision regarding reversal of anticoagulation and consideration for insertion of inferior vena cava filters should be made on an individual basis.

Thrombocytopenia

Thrombocytopenia is a common and well-known phenomenon in cancer, with systemic chemotherapy being the most important contributor (Liebman, 2014). Myeloablative chemotherapy, which is used in stem cell transplant recipients, and the involvement of bone marrow or spleen as a site of cancer/metastasis contribute to the risk (Liebman, 2014). In addition, heparin-induced thrombocytopenia occurs more frequently in patients with cancer than in the cancer-free population (Prandoni et al., 2007).

Thrombocytopenia poses a challenge with anticoagulation due to the competing risks of bleeding and thrombosis. Multiple factors are considered in the thrombocytopenic patient with CAT, carefully balancing the severity of thrombocytopenia versus the risk of thrombosis recurrence or progression (Samuelson Bannow et al., 2018). LMWH is the preferred agent in patients with CAT and thrombocytopenia given the short half-life and ease of dose adjustments. The International Society of Thrombosis and Haemostasis guidance suggests it is generally safe to continue anticoagulation if platelets are above 50×10^9 L^{-1}. If the platelet count drops below this threshold, however, alternate anticoagulation strategies should be considered depending on the patient's individual risk of thrombosis and bleeding (Samuelson Bannow et al., 2018). These include reducing the dose of anticoagulation, temporary cessation of anticoagulation, or maintaining a regular dose with platelet transfusion support as required (Samuelson Bannow et al., 2018).

Treatment failure

Treatment failure may occur in two forms: extension of known thrombosis or the development of a new thromboembolic event while on anticoagulant therapy. The risk of treatment failure is increased three-fold in patients with cancer (Schulman et al., 2015). Prandoni et al. (2002) report a 12-month cumulative incidence of recurrence/extension of 6.8% in patients without cancer and 20.7% in those with cancer, with more advanced disease carrying an almost five-fold risk.

Multiple mechanisms may contribute to the increased risk, including inadequate drug absorption due to poor nutritional intake, chemotherapy, or cancer-related surgery, vomiting, as well as a cancer-induced procoagulable state (Schulman et al., 2015). In addition, patients with squamous cell carcinoma and adenocarcinoma appear to be at a higher risk of anticoagulant failure (Schulman et al., 2015). Treatment failure events are usually addressed by increasing the intensity of anticoagulation or switching to an alternate anticoagulant, most commonly LMWH.

Unprovoked (idiopathic) VTE

Idiopathic VTE presents without a known provoking thrombosis risk factor such as surgery, trauma, estrogen, pregnancy, and/or immobility. An idiopathic VTE presentation raises the possibility of an occult malignancy, as the VTE event may be the first indication of cancer (Carrier et al., 2015). Up to 10% of patients with idiopathic VTE will be diagnosed with cancer within the first year of VTE diagnosis (Carrier et al., 2015). Furthermore, almost 70% of occult cancers are diagnosed shortly after the diagnosis of idiopathic VTE (Carrier et al., 2015).

Although the association with occult malignancy is concerning, there is no evidence to support extensive screening for cancer in this population (van Es et al., 2017). However, it is recommended to ensure that age- and sex-appropriate cancer screening is up to date (Chaput el al., 2021). Screening for prostate cancer and ovarian cancer are not recommended unless red flag symptoms are present (Chaput et al., 2021). Current practice guidelines support the use of thorough clinical assessment including a medical history, review of systems, and presence of constitutional symptoms, as well as assessment of cancer risk factors and red flags. Red flags warrant careful assessment in the context of the clinical presentation because they may be indicative of possible underlying pathology. General constitutional red flag symptoms include unexpected weight loss or gain, loss of appetite, fever, chills, night sweats and/or fatigue or general malaise. The presence of other signs and symptoms may be more specific to the site and type of the suspected cancer. The NICE guidelines for referral of suspected cancer offer a comprehensive and detailed approach to the diagnostic and referral process (https://www.nice.org.uk/guidance/ng12). An interactive flow chart (https://www.nice.org.uk/guidance/ng12/chapter/Recommendations-organised-by-site-of-cancer) for clinical decision making based on site and type of suspected cancer is included.

CONCLUSION

CAT is a frequent and serious complication of cancer. Despite its significance, the awareness of CAT is low in both patients and healthcare providers, with a variation in treatment practices. This article highlights an evidence-based algorithm to manage CAT incorporating risk of bleeding, cancer type, drug-drug interactions and, importantly, patient and clinician preferences. Treatment complications are also outlined, including bleeding, thrombocytopenia, and treatment failure. Finally,

an approach to decisions around cancer investigations in patients with idiopathic VTE is suggested.

The Spot the CLOT series was written with the intent to promote and raise awareness of CAT. Each article in the series focuses on a unique aspect of CAT, including diagnosis, treatment, and awareness. The authors hope this series will help stimulate discussion surrounding CAT among healthcare professionals, patients, and family members, with the ultimate goal of raising awareness and improving patient outcomes.

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