Continuing Professional Development

CPD

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3. PLAN - If I have identified a knowledge gap - will this article satisfy those needs - or will more reading be required?

4. EVALUATE - Did this article meet my learning needs - and how has my practise changed as a result?
Have I identified further learning needs?

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Cancer Associated Thrombosis; clinical challenges and therapeutic advances

60 Second Summary

Cancer associated thrombosis (CAT) is a commonly encountered issue in malignancy and is a major cause of both morbidity and mortality in this population.

The incidence of CAT appears to be increasing and unfortunately has a worse prognosis than thrombosis in the general population. It is in fact the second leading cause of death from malignancy, superseded only by progression of the disease itself.

There appear to be an array of interdependent complex biological mechanisms that exacerbate VTE occurrence in malignancy including aberrant Tissue Factor (TF) expression, endothelial and platelet dysfunction and cancer mediated inflammation but many of these mechanisms remain poorly understood.

Generally, those who are at higher risk from CAT are those with more advanced age, those with a previous history of thrombosis or thrombophilia or immobility.

For the past number of years, following on from the CLOT trial, LMWH has been the mainstay of treatment for CAT, however, recent studies have shown the possible roles for use of DOAC medications in both treatment and prophylaxis of CAT.

VTE is particularly problematic in haematological malignancies given its high rates of occurrence and the difficulties encountered when treating it due to high rates of bone marrow suppression and subsequent thrombocytopenia.

CAT remains a highly significant cause of morbidity and mortality amongst patients with malignancy.

Introduction

Cancer associated thrombosis (CAT) is a commonly encountered issue in malignancy and is a major cause of both morbidity and mortality in this population. Active malignancy accounts for approximately 20% of all cases of VTE[1,2] and is estimated to be responsible for over three million deaths per year[2]. The most common cause of thrombosis in malignancy is venous thromboembolism (VTE) which has an estimated annual incidence of 0.5% in those with cancer when compared with 0.1% in the general population, though naturally this incidence varies both with type of malignancy and aggressiveness of disease[2–4].

The incidence of CAT appears to be increasing[5] and unfortunately has a worse prognosis than thrombosis in the general population[2,6]. It is in fact the second leading cause of death from malignancy, superseded only by progression of the disease itself[2,7]. When compared to cancer patients without thrombosis, patients with CAT have been reported to have a threefold lower survival at 12 months, though this mortality rate was also strongly associated with advanced stage malignancy. There are a myriad of causative factors associated with CAT with research ongoing to understand the biological mechanisms underpinning these links. The advent of Direct Oral Anticoagulant (DOAC) use is beginning to change the treatment landscape of CAT which can now be tailored to each individual, with treatment decisions giving weight to both the type of malignancy and disease activity to ensure the optimal therapeutic option is employed.

Pathophysiology

It has long been recognised that patients with cancer exhibit a hypercoagulable state which is not entirely understood. In 1856, Rudolf Virchow postulated that a triad of conditions lead to thrombosis: endothelial injury, circulatory stasis and abnormalities in blood clotting components[8] and it has been recognised for many years that specific cancers are associated with increased blood viscosity and acquired thrombophilia[2]. There are particular malignancies that appear to display an increased propensity for clotting, namely haematological malignancies and lung, gastro-intestinal (GI), pancreatic and brain cancers. There appear to be an array of interdependent complex biological mechanisms that exacerbate VTE occurrence in malignancy including aberrant Tissue Factor (TF) expression, endothelial and platelet dysfunction and cancer mediated inflammation but many of these mechanisms remain poorly understood[9]. Tissue Factor is a transmembrane protein that acts as a cofactor for Factor VII/VIIa. The TF-FVIIa complex is the primary initiator of blood coagulation and plays an essential role in haemostasis[10]. *In vitro*- many cancer cell lines have been shown to shed TF-positive microvesicles. In patients with malignancy, particularly pancreatic, brain, colorectal and lung cancer, tumour cells appear to release TF-positive microvesicles into the circulation that may contribute to VTE[10–13].

There are an array of other biological mechanisms that have been studied and appear to contribute to hypercoagulability, with most recently, a review by Patmore *et al* highlighting elevated Von Willebrand Factor (VWF) levels which have been found in a variety of malignancies[9,14] and how these elevated levels appear to be an independent risk factor for CAT[15].

It also appears that tumour genetic characteristics have a contributory role in the causation of VTE. Recent studies in genetic profiling have focused on the link between KRAS mutation status and VTE risk. KRAS is a GTPase signalling protein that regulates cell proliferation and survival. It is found to be mutated in approximately 30-50% of colorectal tumours and has

been found in certain studies to be associated with an almost 3-fold increased risk of VTE when compared with patients with wild-type KRAS colorectal cancer[16]. Activating mutations of the KRAS oncogene appear to upregulate tissue factor (TF) expression on colorectal cancer cells and thus, given that TF is a major procoagulant associated with systemic hypercoagulability, it is perhaps no wonder that patients who harbour KRAS mutations have a higher VTE risk. This hypothesis has also been evaluated in other malignancies that are associated with the KRAS mutation, including Non-small cell lung cancer (NSCLC) where the KRAS mutation is commonly seen with small studies reporting that the KRAS mutation appears to be linked with a higher occurrence of VTE[17].

Risk factors

There are a multitude of additional risk factors for CAT and these are generally divided into:

- Patient related factors
- Tumour related factors
- Treatment related factors

There are a number of patient related characteristics that can predispose certain cohorts to CAT. Generally those who are at higher risk from CAT are those with more advanced age, those with a previous history of thrombosis or thrombophilia[18] or immobility. In keeping with the prevalence of thrombosis within specific ethnic groups, CAT also appears more common in black patients and less likely in Asians/ Pacific Islanders[4,19].

There are innumerable treatment related factors that can pre-dispose patients to developing CAT with the most common culprits including surgery, chemotherapeutic agents, hormonal therapy, erythropoietin stimulating agents, anti-angiogenic agents and blood transfusions[4,18]. The placement and use of indwelling access devices such as central venous catheters (CVCs) is also inherently associated with an increased thrombosis risk[5]. Use of chemotherapy accounts for approximately 10% of CAT in this cohort, with agents such as Tamoxifen in breast cancer and L-asparaginase treatment in acute lymphoblastic leukaemia commonly implicated[4]. Very high rates of thrombosis have been reported in multiple myeloma with use of immunomodulatory agents (Lenalidomide, Pomalidomide, Thalidomide) and generally preventative measures such as use of Aspirin or low-molecular weight heparin (LMWH) are employed to try reduce this risk.

Table 1: Khorana Score

Characteristic	Score
Site of Primary Cancer:	
Very high risk (stomach, pancreas, brain)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Haemoglobin <100g/L or use of red cell growth factors	1
Prechemotherapy leucocyte count >11 x 10^9	1
Prechemotherapy platelet count >/ 350 x 10^9	1
BMI >/ 35kg/m^2	1

0= low risk, 1-2 = intermediate risk , >2= high risk

With regards to tumour type, as outlined above, there are certain malignancies that appear to have the highest risk for CAT. Generally pancreatic, brain and lung cancer, in conjunction with haematological malignancies, are widely regarded as high risk for thrombosis[19] whereas malignancies such as breast cancer and prostate cancer appear to have a lower thrombotic potential[19]. It does appear however, that malignancies that present at an advanced stage or behave in a particularly biologically aggressive manner do in fact have a raised thrombogenic potential[19,20] with certain studies listing metastatic disease at diagnosis as the strongest predictor of CAT[20].

Predictive scores for risk

Given the multitude of risk factors for CAT as outlined above, several groups have sought to establish risk scores and strategies for identifying high and lower- risk patients for developing thrombosis. One such score is the Khorana score (Table 1) which is a risk model that was initially developed in an attempt to predict chemotherapy-associated VTE in ambulatory patients with cancer[3]. This score, which is likely the most widely used score, encompasses five predicable variables: cancer site, thrombocytosis pre-chemotherapy, anaemia or use of erythropoietin stimulating agents, leucocytosis and raised BMI. After subsequent validation in further cancer patient cohorts, two laboratory markers, soluble P-selectin (sP-selectin) and D-dimer were added to increase it's predictive value[21]. However, given that sP-selectin is generally not available in routine laboratories, clinical application of the extended tool is limited. The score is endorsed by several guideline groups[22,23] but it's performance remains open to debate, namely in that there are queries as to the positive predictive values of some of the variables i.e. haemoglobin level, white blood cell count and body mass index[24]. In light of this, other groups have sought to establish risk assessment tools for CAT in an attempt to identify high-risk patients that may be suitable for primary thromboprophylaxis. Pabinger *et al* established a simplified score that estimated thrombotic risk based on primary tumour site and D-dimer which did appear to improve discrimination, when compared with the Khorana score[25]. Further studies are needed however to fully validate these results in a clinical setting. Moreover, improved understanding of the biological mechanisms underpinning the pathophysiology of CAT will be of significant clinical importance in the development and refinement of risk assessment tools.

Routine thromboprophylaxis

While prognostic scores may aid the identification of patients at high risk for CAT, the clinical implications of this are not fully clear. The PHACS (A study of Prophylaxis in High risk Ambulatory Cancer Patients) trial was carried out to evaluate the use of LMWH prophylaxis in patients deemed high risk by the Khorana score (>/3). Neither VTE rates or significant bleeding appeared to be particularly different between the prophylaxis and non-prophylaxis group, though this trial was closed prematurely due to poor accrual[26].Naturally, the daily use of LMWH subcutaneous injections also comes with inconvenience and is associated with significant economic cost and thus is often not an enticing option for patients. Recent studies have sought to evaluate the efficacy of direct oral anti-coagulants (DOACs) as primary prophylaxis in cancer patients with a high risk of thrombosis. The CASSINI trial, a randomised, double-blind, placebo-controlled trial compared the efficacy of a prophylactic dose of the DOAC Rivaroxaban 10mg vs placebo in ambulatory cancer patients who were deemed at intermediate-high risk of thrombosis (assigned by the trial as a Khorana score >/2). The patients were screened systematically for VTE and monitored for clinically significant bleeding. Though there were fewer episodes of VTE in the group undertaking prophylaxis, there was not a statistically significant difference compared to the placebo arm. There was a 2% major bleeding rate in the prophylaxis group as opposed to a 1% rate in the placebo group and the authors ultimately concluded that Rivaroxaban prophylaxis did not significantly lower incidence of VTE or death during the trial period(27). The AVERT trial also sought to assess the efficacy of low dosage DOAC use in ambulatory cancer patients with high risk of thrombosis (Khorana score >/2) but this time the DOAC Apixaban at a dose of 2.5mg twice daily was compared to placebo. The primary efficacy endpoint was VTE over a 180-day period with the main safety outcome listed as a major bleeding episode. This study did find a significantly lower rate of VTE compared to placebo control (4.2% vs 10.2%) though higher rates of major bleeding were observed in the treatment group vs placebo (3.5% vs 1.1%). No overall difference in

Study Name	Number of Patients	DOAC	VTE recurrence rates in DOAC arm	Hazard Ratio	VTE rates in LMWH arm	Major Bleeding rates in DOAC arm	Major Bleeding rates in LMWH arm	Hazard Ratio
HOKUSAI VTE	1046	Edoxaban	7.9%	0.71	11.3%	6.9%	4.0%	1.77
SELECT-D	406	Rivaroxaban	4%	0.43	11%	6%	4.0%	1.83
ADAM-VTE	287	Apixaban	0.7%	0.099	6.3%	0	1.4%	*
CARAVAGGIO	1155	Apixaban	5.6%	0.63	7.9%	3.8%	4.0%	0.82

Table 2; Summary of recent clinical trials using DOAC for CAT
*Hazard ratio not estimable because of no bleeding in the Apixaban arm

all-cause mortality was noted[28]. In light of the AVERT and CASSINI trials, international guidelines have now been updated to include consideration for primary thromboprophylaxis in high risk patients with the latest American Society of Clinical Oncologists (ASCO) guidelines stating that thromboprophylaxis with Apixaban, Rivaroxaban or LMWH may now be considered in patients at high risk for VTE. However, due consideration needs to be given to concomitant bleeding risk, possible medication interactions and ultimately patient preference and likely further studies are necessitated to extrapolate which patients will truly benefit from primary thromboprophylaxis.

Treatment

For the past number of years, following on from the CLOT trial[29], LMWH has been the mainstay of treatment for CAT. This pivotal trial compared LMWH in the form of dalteparin to Vitamin K antagonists and found significantly lower rates of recurrent VTE at 6 months (9% vs 17%). It also found a similar rate of clinically significant bleeding between the two groups and thus, for many years, LMWH has been the first choice for most clinicians when faced with treating CAT[29,30]. With the advent of DOACs, treatment of VTE in those without malignancy has completely transformed but this has not, as of yet, fully translated into definitive change in the treatment of CAT. This is likely due to the low numbers of patients with cancer included in the initial DOAC trials which has thus necessitated further studies to examine this specific cohort[30] (Table 2).

The results of two phase III trials which sought to evaluate DOAC use in CAT specifically have been published only recently. The HOKUSAI VTE trial aimed to evaluate the safety and efficacy of Edoxaban, a direct factor Xa inhibitor, compared with treatment with LMWH. The primary outcome was a composite of recurrent VTE and bleeding events and at 12 months, this did not differ significantly between edoxaban and LMWH (12.8% vs 13.5%). However, the study did note a higher rate of gastrointestinal (GI) bleeding in the Edoxaban group, which mainly occurred in those with GI malignancies[31]. A further study, the SELECT-D trial, sought to compare the use of Rivaroxaban, a direct factor Xa inhibitor with LMWH in CAT. This study found a lower rate of VTE in the Rivaroxaban group at 6 months (4% vs 11%) but did noted an increased rate of both major bleeding (6% vs 4%) and clinically relevant non-major bleeding (13% vs 4%). Similar to the HOKUSAI trial, much of this bleeding was GI bleeding and was associated with GI malignancy[32]. Neither study concluded an increased risk in intracranial bleeding with use of Edoxaban or Rivaroxaban[31,32].

Following on from these studies, the ADAM-VTE study was carried out to compare the use of Apixaban, another factor Xa inhibitor, with LMWH in CAT. This study did find lower recurrent VTE rates in the Apixaban group (0.7% vs 6.3%) and very low rates of major bleeding in both the Apixiban and LMWH groups (0% vs 1.4%). These rates were much lower than that seen in the HOKUSAI VTE and SELECT-D trials, which may be explained by the lower overall number of patients enrolled in the trial and also the lower numbers of patients with GI malignancy accrued[33]. Most recently, the CARAVAGGIO study sought to evaluate the use of Apixaban vs LMWH in the treatment of CAT in a larger group of cancer patients. This study concluded that Apixaban was non-inferior to subcutaneous Dalteparin in this cohort with recurrent VTE occurring in 5.6% of the Apixaban group and 7.9% of the Dalteparin group. They did not observe an increased risk of major bleeding with use of Apixaban vs Dalteparin interestingly and rates of GI bleeding were similar. Of note, patients with brain tumours, cerebral metastasis or acute leukaemia were not included in this trial[34].

In light of these findings, several guidelines now incorporate the use of DOACs in the management and treatment of CAT as an alternative to LMWH use. Current European Society of Cardiology (ESC) guidelines advise that use of Edoxaban or Rivaroxaban can be considered for use, particularly in those who do not have GI malignancy and have an anticipated low risk of bleeding[35]. The International Clinical Practice guidelines for treatment and prophylaxis of venous thromboembolism in patients with cancer published in 2019 now advise consideration of Rivaroxaban or Edoxaban in patients who are not at high risk of gastrointestinal/urothelial bleeding and who do not have significant drug interactions[23]. Caution is also advised with DOAC use in patients with Stage IV chronic kidney disease, active/clinically significant liver disease. Other factors that may need to be taken into account when assessing safety and efficacy of use of DOACs in malignancy include chemotherapy -associated nausea/vomiting and surgical resection of the small bowel[36].

General consensus is that treatment dose of LMWH or DOACs should be continued for at least six months for CAT. Strong consideration should be given to continuing the anticoagulation beyond six months if the cancer is still deemed active at this point and can be re-assessed regularly for it's risk-benefit ratio[30,37].

VTE in Multiple Myeloma

VTE is particularly problematic in haematological malignancies given it's high rates of occurrence and the difficulties encountered when treating it due to high rates of bone marrow suppression and subsequent thrombocytopenia. In particular, patients with multiple myeloma, the second most prevalent haematological malignancy[38], have a particularly high thrombotic risk with up to 10% of patients suffering an episode of VTE[39,40]. Multiple myeloma is a bone marrow malignancy that is characterised by the unregulated expansion and accumulation of monoclonal plasma cells/myeloma cells within the bone marrow.

There are multitudes of factors that increase the likelihood of VTE occurrence in multiple myeloma and many appear to be as a consequence of both the disease process itself in addition to the agents that are used to treat the disease. Several groups have sought to evaluate the prothrombotic phenotype in patients with multiple myeloma, common observations include significant elevations in Factor VIII, D-dimer, fibrinogen and Von Willebrand Factor (VWF) antigen in patients with active disease[41–45]. Interestingly, Factor VIII and VWF antigen also appear to be raised, but to a less extreme extent, in Monoclonal Gammopathy of Undetermined significance (MGUS) which is generally regarded as the precursor to multiple myeloma(44). Activated protein C resistance is also a known common phenomenon in multiple myeloma. Generally, Protein C is converted by thrombin into it's active form i.e. Activated Protein C (APC) which has an anticoagulant role. The most common example of APC resistance is due to the Factor V Leiden mutation. However, in multiple myeloma, APC resistance has been found in some studies to occur in up to 10% of patients[46,47] and interestingly, many of these patients do not carry the Factor V Leiden mutation, indicating that this appears to be an acquired APC resistance, in the context of active plasma cell dyscrasia. The full thrombotic potential of the aforementioned coagulation abnormalities has not been fully evaluated as of yet.

In addition to the above, many of the treatment strategies employed in multiple myeloma also increase the likelihood of CAT occurrence. High doses of Dexamethasone are generally utilised in the treatment of multiple myeloma, usually

in combination with additional agents. Several studies have shown that the addition of high dose steroids to a chemotherapy regimen is associated with a significantly increased thrombosis risk[39,48]. The exact causative mechanism of this is unclear, though there is some *in vitro* evidence that Dexamethasone can stimulate the endothelium to increase expression of tissue factor, cellular adhesion modules and VWF[49]. Dexamethasone is commonly used in combination with immunomodulatory agents such as Lenalidomide, Pomalidomide and Thalidomide and appears to enhance their thrombogenic potential, though these agents in themselves, are associated with an increased VTE risk[39,50,51]. Indeed, the International Myeloma Working Group (IMWG) now recommends that a VTE risk assessment should be carried out in all patients receiving immunomodulatory agents and either aspirin or LMWH prophylaxis is recommended, depending on the risk factors present[52]. There is no widely used multiple myeloma specific thrombotic risk score in use at present, though certain groups have validated scores e.g. the myeloma clot score, MCS[53] in an attempt to standardise this evaluation.

Conclusion

CAT remains a highly significant cause of morbidity and mortality amongst patients with malignancy. The era of DOAC medications has undoubtedly started to change the landscape of treatment for thrombosis in cancer. However, further studies are necessitated to fully understand the biological mechanism underpinning the pathophysiology of CAT so that appropriate thromboprophylaxis can be optimally employed in order to ultimately prevent this devastating condition in cancer patients.

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