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Cancer-associated thrombosis (CAT) - New challenges for the hematologist - Section 3

Cancer associated thrombosis: Which lessons for the hematologist?

Simon Noble

Marie Curie Palliative Care Research Centre, Cardiff University, Cardiff Wales, UK

Take Home Messages

- The current data supports LMWH as the first line management of CAT.
- New data shows that DOACs have a lower rate of VTE recurrence but this comes at an expense of major bleeding
- Major bleeding on DOACs is most marked in gastrointestinal and urothelial tumors.
- Patients should be involved in the decision making around which anticoagulant to use, taking into account their values and preferences.
- DOACS should be used with caution if patient is taking other drugs which inhibit/ induce p-glycoprotein and or CYP3A4.

Abstract

The past fifteen years has seen major developments in the management of cancer-associated thrombosis (CAT). Warfarin, once the mainstay of anticoagulation, has been superseded by low molecular weight heparins. More recently, data from the direct acting oral anticoagulants (DOACs) suggest a role for these new agents as well. No longer, is the management of a highly complex pathophysiological process limited to one agent. Hematologists are now faced with a breadth of approaches, which may be individually chosen according to the patient's clinical condition, future anticancer treatments and patient values. Furthermore, developments in the management of CAT have occurred alongside significant advances in the management of cancer itself; patients with metastatic disease are living and receiving chemotherapy for longer ever before. This brings further challenges for the clinician; particularly with respect to deciding how long to continue anticoagulation and with which agent. This paper shall focus on key lessons for the hematologist including how venous thromboembolism differs in the malignant state, patient perspectives, the role of DOACs, and management where the evidence is lacking. Finally, it shall explore the importance of understanding patient preference and values when agreeing on patient centered management.

Introduction

The management of cancer-associated thrombosis (CAT) has developed considerably over the past two decades and with cancer therapies keeping patients with metastatic disease alive longer, hematologists will face new challenges in the supportive care of this vulnerable population. This brief paper will focus on a few new areas of interest with lessons of interest to the hematologist.

Venous thromboembolism differs in the malignant state

The epidemiology and pathophysiology of CAT has been extensively described.[1] Whilst venous thromboembolism (VTE), in the non-cancer setting, usually occurs as the result of a temporary increase the thrombotic state, the thrombogenicity associated with CAT usually persists as long as the cancer is present and will wax and wane according to changes in therapies and disease status. In addition to VTE being more common in the malignant state, the structure of the clots they form also differs. Recent research has suggested that the malignant state leads to the formation of far denser clots. One study has shown that patients with stage IV lung cancer will form clots of 4 times the density of patients with early stage disease.[2])

The patient perspective in CAT

The physical symptoms of VTE are well established; although classic symptoms such as dyspnea, chest pain and leg edema may be attributed to the cancer itself and not thrombosis. Qualitative data have identified the experience of CAT to be an extremely distressing one with ongoing psychological sequelae.[3,4] Some patients report the experience of CAT to be more distressing than the cancer itself. Of particular note are the information needs of patients; few are aware that CAT may be precipitated by chemotherapy or the red flag symptoms, which would necessitate medical attention.[5]

Direct acting oral anticoagulants (DOACs) and cancer

Data from randomized control trials (RCTs) comparing warfarin with LMWH in the treatment of CAT have demonstrated the superiority of LMWH over warfarin in preventing VTE recurrence without increasing bleeding risk.[6] Consequently, clin-

ical guidelines recommend three to six months weight-adjusted LMWH for the first-line treatment of CAT.[7,8] The launch of the oral factor IIa inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban offer new options in the management of VTE.[9-13] These direct acting oral anticoagulants (DOACs) have demonstrated non-inferiority with warfarin for the treatment of conventional VTE and some show a superior safety profile with respect to major bleeding. Requiring no monitoring or dose adjustments and with significantly fewer drug-drug interactions than warfarin, the DOACs could potentially offer an attractive alternative to current practice.[14]

Two RCTs have recently been reported, comparing a DOAC with LMWH in the treatment of CAT.[15,16] The SELECT-D pilot study, compared rivaroxaban with dalteparin for the treatment of CAT. Over 400 patients were recruited. The VTE recurrence rate at 6 months was 11% (95% CI 7-17%) for patients on dalteparin and 4% (95% CI 2-9%) for patients on rivaroxaban. Major bleeds were similar across trial arms [6 bleeds from 6 patients (3%; 95% CI 1-6%) on the dalteparin arm; 9 bleeds from 8 patients (4%; 95% CI 2-8%) on the rivaroxaban arm]. There were more clinically relevant non-major bleeds (CRNMBs) on the rivaroxaban arm; 5 bleeds from 5 patients (2%; 95% CI 1-6%) on dalteparin compared with 28 bleeds from 27 patients (13%; 95% CI 9-19%) on rivaroxaban. In total, 11 patients (5%; 95% CI 3-9%) on the dalteparin arm had bleeds categorised as either major bleeds or CRNMBs compared to 34 patients (17%; 95% CI 12-22%) on the rivaroxaban arm. The HOKUSAI VTE Cancer study compared 5 days LMWH followed by edoxaban 60 mg once daily with dalteparin at a dose of 200 IU/kg for 1 month followed by dalteparin 150 IU/kg in cancer patients with VTE. The primary outcome was a composite of recurrent VTE and major bleeding.[16] 1046 patients were recruited. Edoxaban demonstrated non-inferiority with dalteparin with a primary-outcome event in 67 of the 522 patients (12.8%) in the edoxaban group with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P=0.006 for non-inferiority; P=0.87 for superiority). It appears that edoxaban results in fewer recurrent VTE events, at the expense of more major bleeding episodes. Recurrent VTE occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, -3.4 percentage points; 95% CI, -7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group

Table 1. **Common drug-drug interactions with Direct Acting Oral Anticoagulants; based on(18).**

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Interaction effect	P-glycoprotein	P-glycoprotein CYP3A4	P-glycoprotein CYP3A4	P-glycoprotein
Increases DOAC plasma levels†	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib
Reduces DOAC plasma levels‡	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine

†Drugs that inhibit P-GP or CYP3A4 can increase DOAC levels; ‡Drugs that induce P-GP or CYP3A4 can lower DOAC levels.

Table 2. **Management of challenging cases of CAT: ISTH SSC recommendations.[25]**

Recurrent VTE despite anticoagulation

1. If on warfarin, switch to therapeutic LMWH
2. If already on LMWH, increase dose by 25% or increase back up to therapeutic weight adjusted dose if they are receiving non-therapeutic dosing.
3. If no symptomatic improvement, use peak anti-Xa level to estimate next does escalation

Management of CAT in thrombocytopenia

1. For platelet count > $50x10^9$ L^{-1} give full therapeutic dose LMWH
2. For acute CAT and platelet count <$50x10^9$ L^{-1}
   a. Full anticoagulation with platelet transfusion to maintain platelet count >$50x10^9$ L^{-1}
   b. If platelet transfusion not possible consider retrievable IVC filter
3. For subacute or chronic CAT and thrombocytopenia (platelet count <$50x10^9$ L^{-1})
   a. Reduce therapeutic dose by 50% or use prophylacitic dose for platelet count 25 - $50x10^9$ L^{-1}
   b. Omit LMWH if platelet count <$25x10^9$ L^{-1}

Bleeding whilst anticoagulated

1. Assess each bleeding episode to identify bleeding source, severity, impact and reversibility
2. Provide supportive measures to stop bleeding including transfusion where indicated
3. For a major or life-threatening bleeding episode: withhold anticoagulation
   a. Consider IVC filter insertion in patients with acute or subacute CAT with a major or life-threatening bleeding episode
   b. Do not consider IVC filter insertion in patients with chronic CAT
   c. Once bleeding resolves: remove retrievable filter (if inserted) and resume/ initiate anticoagulation

(difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6). Major bleeding was higher in gastrointestinal (13.1%) and urothelial (7.9%) cancers and it would seem unreasonable to use DOACs to manage CAT in such cancers. Such an approach is reflected in the clinical practice in the Memorial Sloan Kettering Cancer Center.[17] This policy appears to be safe, with a much lower major bleeding rate (2%).

A final issue worthy of consideration lies with the potential for drug-drug interactions.[18] DOACs, whilst subject to fewer interactions than warfarin, are particularly sensitive to medicines, which inhibit P-Glycoprotein or cytochrome P450 3A4 (CYP3A4). These include chemotherapies and supportive care medicines commonly used in oncology (Table 1). Nevertheless, if patients are unable to take a LMWH, DOACs may be a better choice than warfarin. However, patients need to be aware of the limitations of data and the possible risks should they choose to take DOACs for the treatment of CAT.

Where the evidence is lacking

The heterogeneity of CAT goes beyond the different thrombogenicities and risk factors for VTE, conferred by each tumor type and chemotherapy regime. All of the LMWH studies in CAT had exclusion criteria; patients with poor performance status, life expectancy of less than three months, thrombocytopenia, increased bleeding risk, renal impairment, and weight less than 40 kg.[19-22] Recurrent VTE is seen most commonly in those with advanced disease, in particular lung, ovarian, brain and pancreatic cancer.[23,24] Up to 21% of CAT patients are managed outside of the standard treatment of weight adjusted LMWH. These include patients with recurrent VTE despite anticoagulation, patient with thrombocytopenia, and those with bleeding complications. The management of such cases is covered in a guidance document recently published by the International Society for Thrombosis and Haemostasis Scientific Sub-Committee (ISTH SSC) for Malignancy and Haemostasis.[25] However, it important to recognize that not all patients will be adequately managed with standard weight-adjusted LMWH and such situations are summarized in Table 2.

Patient preference and values

Treatment decisions regarding CAT are most often made without the patient's involvement. This is particularly prevalent in cancers like advanced pancreatic, stomach or brain cancer, all highly prothrombotic conditions. Paternalistic nihilism often dominates management with perceptions of self-injection being unacceptable dominating decision-making.[26] This directly contradicts qualitative data, which concluded LMWH to be an acceptable intervention.[21] Patients have reported efficacy of treatment to be most important paramount despite the hypothetical preference of a tablet over an injection.[4] This finding was also highlighted in the recent choice based experiment study,[27] where patients valued safety, efficacy, and lack of interference with anticancer therapies ahead of method of administration. In this study of a cohort of 100 cancer patients receiving long-term anticoagulation, only 13% of patient preferred oral to subcutaneous route. Thirty-nine percent prioritized strategy that had minimal interference with their anti-cancer therapy, 25% favored strategy with better efficacy (24%) and 19% with low risk of adverse events. These data, whilst very informative, should be viewed in the context of the participants interviewed; namely patients receiving anticoagulation for an average of 6 months. Personal experience would suggest the acceptability of LMWH changes over time and it is not unusual for patients to require indefinite anticoagulation. After an initial dislike of an injection, many patients get used to it and normalize their injection through ritualization. However, a proportion of patients will tire of injections over time, especially those with low body fat or a tendency to develop subcutaneous lumps. It is becoming more common to see the choice of anticoagulant changing over the cancer the journey, in order to optimize quality of life, without addition risk to safety.

Anticancer effects of anticoagulants

The coagulation cascade and certain mechanisms of metastatic progression are inextricably linked, with particular focus on the activities of tissue factor, thrombin generation and the selectins. *In vitro* and *in vivo* data furthermore suggest the LMWHs may inhibit various mechanisms of metastasis progression including endothelial adhesion, angiogenesis and P-selectin activity in maintaining the micro-metastasis structure.

Secondary analyses of clinical trials involving LWMHs have supported this hypothesis, with potential survival benefits most marked in early disease.

However, despite several well-designed, adequately powered prospective RCTs, there is no data to support the theory that LMWHs or indeed any antithrombotics have sufficient anti-cancer effects to have any clinical utility with respect to survival or time to disease progression.(28) Whilst there are still a few trials completing at the moment, the hope that antithrombotics may pay a significant role in the treatment for cancer are diminishing.

Conclusion

The management of CAT remains an exciting and challenging area that is rapidly becoming recognized as a unique subspecialty of hematology. As further data emerges, DOACs are likely to have a greater role in their management, which will increasingly need to consider patients' preferences and values.

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