Gloucestershire Hospitals
NHS Foundation Trust

Cancer associated thrombosis (CAT) guideline (solid tumour malignancy)

Contents

1. Introduction

Venous thromboembolism (VTE) is a major complication of cancer (occurring in 4%-20% of patients) and is one of the leading causes of death in patients with cancer. The risk is greatest for patients who are hospitalised and/or receiving active treatment. Certain tumour sites (Upper GI, hepatobiliary, lung and gynaecological) and treatment regimens (bevacizumab) have reported very high rates of VTE.

Patients with cancer associated VTE have a higher risk of recurrence on treatment than those without cancer.

Many patients with cancer associated VTE (CAT) can be managed as an outpatient and may present to a variety of clinical areas including:

- GP
- Outpatients
- Acute Haematology and Oncology Unit (AHOU)
- Ambulatory care
- Emergency and urgent care departments

2. Investigation

All patients with suspected cancer-associated VTE should undergo the following investigations:

- Baseline FBC, U&Es, LFTs and coagulation screen
    - Particularly important if patient is on bone marrow suppressive treatment as at increased risk of thrombocytopenia
    - Patients with cancer-associated VTE are at increased risk of adverse bleeding events
    - D-dimer is not a validated test in a patient with a known malignancy and should not be routinely performed
- Relevant imaging – aim within 24 hours
    - CTPA
    - Lower limb USS via general USS.
    - Upper limb USS via vascular lab (refer on ICE, but discuss directly with vascular studies)
- If incidental finding on scan asses to see if clinically stable and organise for bloods and anti-coagulation – if unwell/OOH can be seen for assessment in AHOU

3. Management

When assessing the appropriateness of anticoagulation, it is essential that the clinical state, patient's prognosis and risks of anticoagulation are taken into account. When in doubt regarding any of these factors, a discussion with the patient's consultant and patient themselves are of paramount importance. If the patient is in a non-specialist area (e.g. not under Oncology) then contact should be made with the Acute Oncology Service (AOS) via the appropriate e-referral, or in emergencies via bleep 1190, if there is any doubt regarding any of the above factors.

3.1 Pre-imaging

- If there is a strong clinical suspicion then treatment should be commenced prior to imaging
    - High Well's score
    - History of VTE
    - Other diagnosis unlikely
    - Patient at risk of clot progression
- For most patients it is appropriate to give anticoagulation whilst awaiting imaging.

3.2 Confirmed VTE

3.2.1 DOACs

DOACs (specifically: apixaban, edoxaban or rivaroxaban) are an acceptable alternative to LMWH for the treatment of CAT in specific patients with a low risk of bleeding and where there are no anticipated drug-drug interactions with their anti-cancer therapy or other contraindication (C/I) (See individual SPCs/BNF for further information).

In appropriate patients a **DOAC should be considered as first line.**

Cancer patients with a high risk of bleeding and who should be considered for treatment with LMWH rather than a DOAC include patients with:

- GI cancers (particularly upper GI) e.g. oesophageal or gastric cancer. Apixaban can be considered in patients with lower GI cancers e.g. colorectal cancers as similar risk of bleeding *vs*. dalteparin.
- Urothelial cancers

Other reasons for using a LMWH over a DOAC may include:

- History of GI bleeding
- Frequent emetogenic chemotherapy, nausea and vomiting, difficulty with oral intake
- Concerns for GI absorption (feeding tubes, gastric or bowel resections)
- Likely thrombocytopenia expected secondary to cancer/ anti-cancer treatment
- Pancreatic cancer
- Previous recurrent VTE on a DOAC or LMWH
- Patients with a primary brain tumour or brain metastases

There is little information regarding the effect of DOACs on anticancer drugs. None of the DOACs are inhibitors or inducers of CYP3A4, P-gp or BRCP. Consequently, they are unlikely to affect the pharmacokinetics of other substrates including anti-cancer drugs.

There is limited evidence on the effect of anti-cancer agents on DOACs. Information is largely theoretical. Potential interactions may occur particularly with drugs which are either inhibitors or inducers of CYP3A4 and/or p-gp. The following anti-cancer agents may theoretically effect plasma concentrations of DOACs and LMWH may be more appropriate. Please note that this is not an exhaustive list and use of a DOAC is not necessarily contraindicated. Please discuss patients on any of the following agents who are being considered for treatment with a DOAC with pharmacy/medicines information

Inhibitors (enhance anticoagulant effects, increase risk of bleeding)

- Imatinib
- Crizotinib
- Vemurafenib
- Bicalutamide
- Encorafenib

Inducers (reduce anticoagulant effects, increase risk of thrombosis)

- Enzalutamide
- Bexarotene
- Paclitaxel (not docetaxel)
- Encorafenib
- Dabrafenib

3.2.2 Dosing information

Apixaban: 10mg BD for 7 days then 5mg BD. Avoid if CrCl <15ml/min

Edoxaban: Weight ≤61kg 30mg OD**,** >61kg 60mg OD**.** CrCl 15-50ml/min 30mg OD**,** avoid if CrCl<15ml/min.
Precede with 5 days LMWH

Rivaroxaban: 15mg BD for 21 days then 20mg OD. Must be taken with food. Reduce maintenance dose to 15mg if CrCl 15-29ml/min. Avoid if CrCl < 15ml/min.
Apixaban and rivaroxaban should start 24 hours after last dose of therapeutic dalteparin.

LMWH (dalteparin)
Dalteparin is currently the only licensed LMWH for cancer associated thrombosis and then only for a six month period.

Contraindications to LMWH: (See the British National Formulary (BNF)/ summary of product characteristics (SPC) for full list).

- Known or suspected hypersensitivity to dalteparin or other LMWHs and/or heparin
- History of heparin induced thrombocytopenia (HIT)
- Significant hepatic impairment
- Active gastric / duodenal ulceration or oesophageal varices
- Haemophilia and other inherited/major bleeding disorders
- Thrombocytopenia
- Recent (within 3 months) cerebral haemorrhage (except stroke due to systemic emboli)
- Severe hypertension
- Recent neurosurgery and eye/ear surgery and injuries to the CNS/eyes and ears
- Subacute endocarditis

3.2.3 Dosing regimen

Month 1

Administer Dalteparin 200 units/kg total body weight subcutaneously ONCE daily for first 30 days of treatment (see table below).

Body Weight (kg)	Dose (units)
<46	7500
46-56	10000
57-68	12500
69-82	15000
≥83	18000

Months 2-6

Administer Dalteparin 150 units/kg subcutaneously ONCE daily (see table below).

Body weight (Kg)	Dose (units)
<56	7500
57-68	10000
69-82	12500
83-98	15000
≥99	18000

In some patient groups it may be appropriate to continue with the full therapeutic 1 month dose of dalteparin beyond the first month. For example:

- Patients with a PICC line associated DVT
- Patients with an additional indication for anticoagulation (e.g. atrial fibrillation)
- Patients with pancreatic cancer
- Patients with recurrent VTE

3.2.4 Administration

On initiation ensure the patient or care giver is able to administer dalteparin correctly and is supplied with a yellow sharps bin to dispose of used needles.

3.2.5 Renal failure / extremes of body weight

Therapeutic LMWH should be used with caution in patients with renal impairment and dose reduction or anti-Xa monitoring may be indicated in patients with a **GFR < 30ml/min**.

Enoxaparin 1mg/kg daily should be used if CrCl<30. Anti-Xa activity monitoring can be considered, particularly if CrCl<15. See below for further advice on timing and normal ranges. If in doubt, discuss with haematology.

In patients at extremes of body weight (patients either <45kg or >120kg) then anti-Xa monitoring may be required with subsequent dose adjustment. Discuss with haematology if needed. Consider dosing dalteparin as per actual body weight (i.e. 100 units/kg TWICE daily) if > 120kg.

3.2.6 LMWH monitoring

Anti-Xa levels should be taken 3-4 hours post dose (peak level) after the 3rd of 4th dose. This should be taken in a citrate (blue top) tube.

The target range for anti-Xa levels in patients receiving **therapeutic dose** LMWH is **0.5-1.0 units/ml** for ONCE a day dosing.

3.2.7 Anticoagulation with thrombocytopenia

Requires careful assessment of thrombotic risk vs bleeding risk:

- **Plt >50x10^9/l** – Full anti-coagulation (monitor for bleeding)
- **Plt 25-50x10^9/l** – If high thrombotic risk (e.g. thrombotic event within last 3 months) use prophylactic anticoagulation (monitor for bleeding)
- **Plt <25x10^9/l** – Avoid anticoagulation

Consider platelet transfusion to maintain platelets >50x10^9/l if thrombosis within last 4-6 weeks (Discuss with haematology)

3.2.8 Duration of treatment

This should be reviewed by the oncology team or clearly communicated to the GP (in the form of a letter) if the patient will not be regularly seen by Oncology. The default should be that this is reviewed by the oncology team.

Review at 3 months:

- If patient asymptomatic and cancer not active (off treatment) then treatment can be stopped as considered a provoked VTE
- Otherwise continue to 6 months – if on LMWH consider switching to DOAC if appropriate

Review at 6 months

- If cancer not active and not on treatment then can be stopped
- If cancer remains active the CLOT trial recommends considering lifelong anticoagulation – this is a personalised choice and should take into consideration thrombotic risk, bleeding risk and patient preference.

  If decided to continue then some patients may benefit from a reduced intensity anticoagulation, e.g. Apixaban 2.5mg BD.

  In uncomplicated patients there is no evidence for continuing LMWH beyond 6 months and they should be switched to a DOAC

3.3 PICC line associated DVT

Consider if PICC line still required

Should be removed if:

- Line associated infection
- Poorly functioning
- If symptoms persist once anti-coagulated

If line remains in situ anticoagulation should be continued for 3 months and/or until line removed (choice of anticoagulant as above).

If line removed then anti-coagulation should continue for at least 6 weeks from removal to reduce risk of embolization. If not possible due to clinical situation avoid removal OOH unless the patient is septic (Ideally following 24 hours of anti-coagulation to reduce the risk of clot embolization).

Further information about management of CVC associated VTE available here: https://spcare.bmj.com/content/11/4/371

3.4 Anti-coagulation of primary and secondary brain tumours

Patients with primary and secondary brain tumours require a cautious approach towards anticoagulation due to a propensity for bleeding and the risks of bleeding within an enclosed space. However, presence of active intracranial malignancy is not a contraindication to anticoagulation. Either a DOAC or LMWH can be considered in the absence of haemorrhage or thrombocytopenia. If in doubt, this should be discussed with the patient's consultant.

3.5 Patients with progressive/recurrent venous thrombosis despite anti-coagulation

Consider the cause – including progression/relapse of underlying malignancy
General approach:

1. Check compliance with current anti-coagulation.
2. If recurrent VTE on a DOAC, switch back to LMWH. If recurrent VTE or LMWH, then increase back to full dose or check drug levels (e.g. factor Xa level).
3. Any concerns discuss with haematology

3.6 Management of incidental CAT

Many CATs are identified incidentally on staging or diagnostic imaging and most can be managed as per the usual guidance.

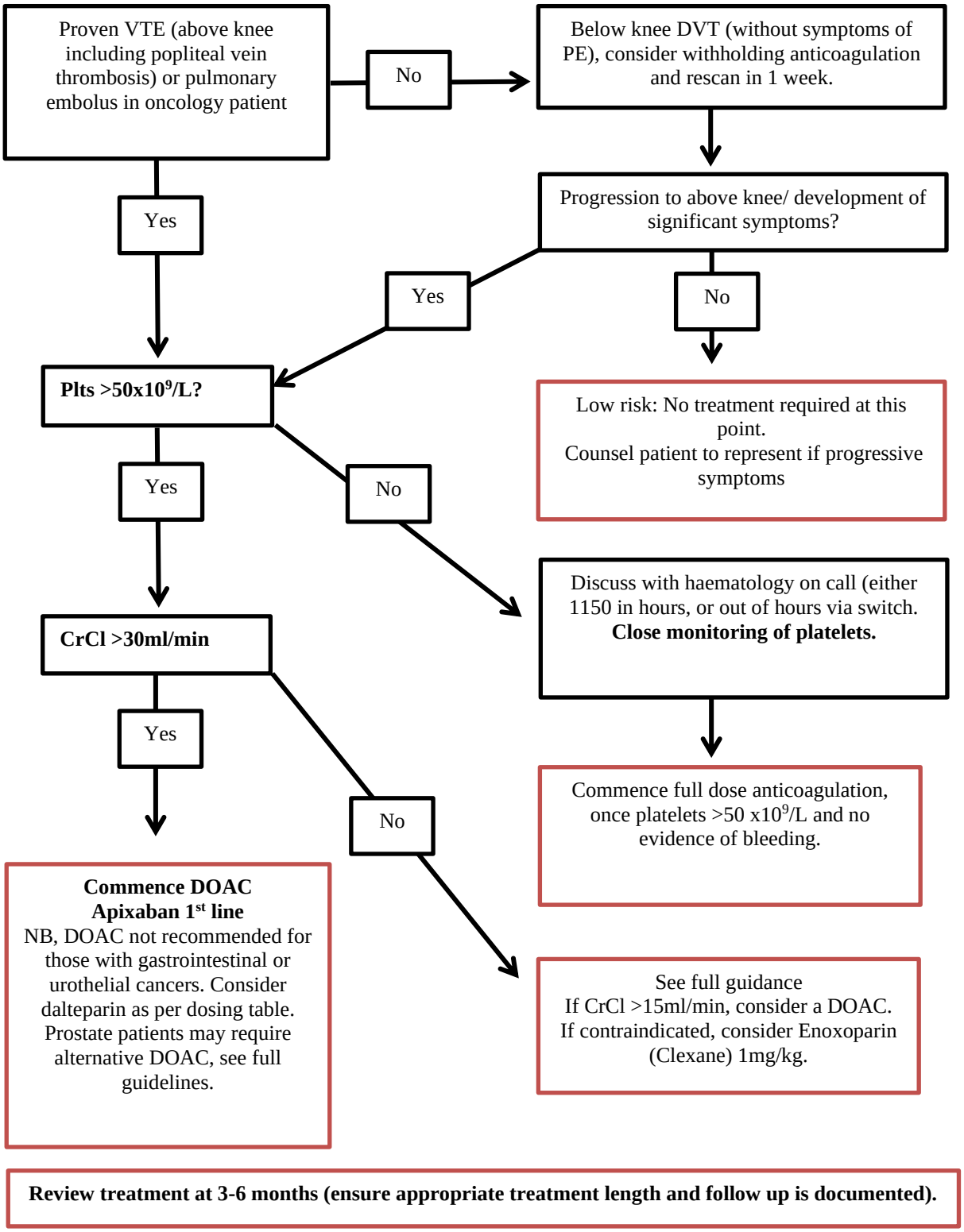
If a patient has active cancer and a small sub-segmental PE is demonstrated on imaging, then anticoagulation should be considered, taking into account; bleeding risk, patient prognosis and clinical state.

3.7 Documentation and follow-up

If a patient is diagnosed with CAT in AHOU or during admission then a clear follow up plan and notification to the GP must be made.

1. For AHOU:
    a. Clear documentation on chemocare
    b. Discharge with 28 days supply of anti-coagulation
        i. If OOH then can return for prescription next day or have FP10
    c. Ensure patient is counselled for bleeding risk
    d. Complete template letter and email to Kathy Brown (Kathy.brown4@nhs.net) (who will turn into a letter for GP)
        i. Include length of treatment if known
        ii. Clear dose of anticoagulation for GP to continue – *may be different if using dalteparin*
2. For inpatient diagnosis:
    a. Please include clear details of CAT in discharge summary
        i. Including length of treatment if known
        ii. Clear dose of anticoagulation for GP to continue – *may be different if using dalteparin*
    b. Ensure suitable follow up made at discharge

4. Cancer Associated VTE Flowchart.



Review treatment at 3-6 months (ensure appropriate treatment length and follow up is documented).

Gloucestershire Hospitals
NHS Foundation Trust

5. Sample VTE diagnosis letter

Acute Haematology and Oncology Unit
Gloucestershire Oncology Centre
Cheltenham General Hospital
Sandford Road
Cheltenham
GL53 7AN
Email: *Generic AHOU email*

GP address
Date:

Dear colleague,
RE: *Patient details*

The above patient has recently been reviewed on AHOU and diagnosed with a (*tick appropriate box*):

Left ☐ Right ☐N/A ☐

DVT ☐ PE☐ PICC associated VTE ☐ Other☐

Arm ☐ Leg☐ N/A☐

They have been started on:

Drug:	Dose:
Instructions:	
Amount given:	

It will be reviewed by:

Who:	When:

Any further instructions:

We would appreciate you continuing to prescribe this until further notice.

If you have any further questions or concerns, please do not hesitate to contact us.
Best wishes,

AHOU team.
CC' patient's responsible consultant