Guidelines for the Use of Low Molecular Weight Heparins (LMWH) and Direct Oral Anticoagulants (DOACs) in adults with cancer / malignancy

Venous Thromboembolism (VTE) Prophylaxis / Prevention

a) In-patients and surgical patients

See local Trust policies for details - all hospitalised patients should be assessed on admission for VTE risk, and all cancer patients with reduced mobility should be prescribed LMWH, in the absence of bleeding or other contra-indications.
(Data is inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or brief infusional chemotherapy)

b) Out-patients

Routine VTE prophylaxis of ambulatory cancer patients is not recommended, with the exception of patients receiving thalidomide, lenalidomide or pomalidomide.
For patients prescribed thalidomide, lenalidomide or pomalidomide, the options are either:

- prophylactic dose of LMWH (e.g. dalteparin 5000 units SC od or enoxaparin 40mg SC od)
  or
- low dose aspirin (75 - 150mg od), if LMWH considered unsuitable

(There is limited data for the use of apixaban in this setting, but it is not recommended as an option in any national guidelines)

The duration of thromboprophylaxis should be guided by risk factors such as active disease (e.g. for the first 4–6 months of treatment until disease control achieved), and then de-escalated or discontinued unless there are ongoing significant risk factors.

Stroke Prevention

Patients established on warfarin or direct-acting oral anticoagulants (DOACs) for stroke prevention (e.g. patients with AF), and about to start chemotherapy

All patients on warfarin should be switched to edoxaban, unless contra-indicated.

If edoxaban is not considered appropriate, instead switch to LMWH.
There is no published evidence regarding the dose of LMWH to be recommended for this patient group, but it is suggested that the VTE treatment dose is the most appropriate (for dalteparin, 200IU/kg)

Patients with luminal GI cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active GI mucosal abnormalities such as duodenal ulcers, gastritis, oesophagitis or colitis are probably best treated with LMWH.

DOACs should be used with extra care / consideration of dose, if CrCl < 50ml/min, or LFTs > 2 x ULN, or clinically significant drug interactions.

DOACs are not recommended if expected malabsorption in stomach or small bowel.

*Edoxaban is the preferred DOAC in Surrey for patients with AF, as most cost effective; for Sussex patients, any DOAC may be used*
Treatment of established Venous Thromboembolism (VTE)

All PROVEN pulmonary emboli should be assessed by acute medicine.

Ilio-femoral DVTs, and proximal DVT with grossly swollen legs impairing mobility, or phlegmasia, should be discussed with vascular surgery, regarding catheter-directed thrombolysis

Anticoagulation:

a) LMWH

LMWH at treatment dose is the recommended treatment for cancer patients with established VTE. Cancer patients initiated on anticoagulation by medical teams outside of oncology will routinely be started on a LMWH.

Choice of LMWH is made at Trust level; options include dalteparin, enoxaparin and tinzaparin. For dalteparin in cancer patients, the dose should drop down after 30 days from 200IU/kg to 150IU/kg.

b) DOACs

Rivaroxaban or edoxaban may be considered in patients with an acute diagnosis of VTE, a low risk of bleeding, and no interactions with current systemic therapy. Rivaroxaban or edoxaban may also be considered for suitable patients initiated on LMWH, but who are unable to tolerate LMWH injections, or who wish to avoid further LMWH injections.

Preliminary data¹ ² in cancer patients show that rivaroxaban or edoxaban may be as effective as LMWH, but they cause more bleeding. Bleeding appears mostly in patients with upper GI or genito-urinary tract cancers.

This data should be discussed with patients to assist decision-making.

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Duration of treatment

- Anticoagulation should be given for at least 6 months in cancer patients with established VTE.
- Anticoagulation will generally stop at 6 months in patients whose cancer is considered cured at this point.
- In patients whose cancer remains active after 6 months (includes patients being monitored, managed expectantly, on treatment, or with progressive disease) continuation of anticoagulant therapy should be considered.
Special cases:

a) **Patients established on warfarin for treatment of VTE, and then referred for chemotherapy**

If VTE diagnosed within the previous 6 months, the patient should be switched to a treatment dose of LMWH*, or a DOAC** (see Treatment of established Venous Thromboembolism above, for information on decision-making).

This is irrespective of the chemotherapy regimen or stage of cancer - even if the cytotoxics do not interact with warfarin, there may well be loss of INR control due to side effects of chemotherapy, e.g. diarrhoea, nausea, anorexia, or changes in diet.

If VTE diagnosed more than 6 months ago, consider switching to a DOAC for suitable patients (for rivaroxaban, start at the maintenance dose) - but caution in patients at high risk of bleeding (again, see above).

*if using dalteparin, starting with the Month 2 dose of 150IU/kg is reasonable if VTE > 1 month previously.
**for rivaroxaban, start with maintenance dose if VTE > 3 weeks previously

b) **Patients established on a DOAC for treatment of VTE, and then referred for chemotherapy**

 Leave on the DOAC, unless issues with oral intake, absorption, or drug interactions.

c) **Recurrent VTE while on treatment dose LMWH**

Always consider heparin-induced thrombocytopenia (HIT), as this pre-disposes to thrombosis – check platelet count and discuss with haematologist if concerns.

For management of patients with recurrent VTE while on full treatment dose of LMWH (e.g. dalteparin 200 IU/kg/day), there is no published data, but it is accepted standard practice to consider increasing the dose of the LMWH by 25%-30%, with the total daily dose split into two equal doses, administered morning and evening. Aim to round dose to nearest pre-filled syringe size.

Re-assess after 5 – 7 days. If no clinical improvement, check anti Xa level (at 4 hours post dose) and consider dose escalation in discussion with haematology.

d) **Recurrent VTE while on a DOAC**

Switch to standard dose LMWH (200IU/kg dose, for dalteparin).
Re-assess after 5 – 7 days.

e) **Platelet count falls while on anticoagulation**

*N.B. If platelet count falls with no explanation in patients on LMWH, consider heparin-induced thrombocytopenia (HIT) and discuss urgently with haematologist.*
• **Patients on anticoagulant as stroke prevention in atrial fibrillation**
  Decision to withhold anticoagulation due to thrombocytopenia must be individualised based on the patient’s thrombotic risk (e.g. stroke in previous 3 months puts patients had particularly high risk for recurrent stroke).
  In general, consider holding anticoagulation if platelet count falls to < 75 on chemotherapy, or if there is bleeding.
  Patients with previous chemotherapy-induced thrombocytopenia, or on especially myelosuppressive chemotherapy will require particularly close monitoring.

• **Patients on anticoagulation for VTE**
  In the absence of bleeding, therapeutic dose LMWH may be used, down to a platelet count of 50 x 10^9/l.
  If platelet count drops to < 50 within 4 weeks of an acute VTE, the platelet count should be maintained at > 50 with transfusion, and therapeutic doses of LMWH continued.
  If most recent VTE was more than 4 weeks ago, reduce to prophylactic dose of LMWH if platelet count 30 – 50 x 10^9/l. And discontinue LMWH if platelets fall to < 30 x 10^9/l.

f) **Catheter-related thrombosis**

Line does not necessarily need to be removed if it is functional, required, not infected and there is no contra-indication to anticoagulation.

• In the absence of contra-indication, therapeutic LMWH should be given for a minimum of 3 months, or longer if the line is to remain in situ (continue until line removed)
• If the line is to be removed, anticoagulation for 3-5 days before removal is recommended.
• Anticoagulation should still continue for 3 months, unless bleeding risk contra-indicates this.
• If bleeding risk makes anticoagulation undesirable, catheter removal without anticoagulation can be considered.
• In cases of severe symptoms or SVC involvement, discuss with vascular surgery for consideration of thrombolysis.

References:
Lyman, G et al; JCO 2007; 25: 5490 -5505 (ASCO)
Kuderer, N et al; Thromb Res 2014; 133: S122 - S127 (ASCO)
Lee, AYY et al; NEJM 2003; 349: 146 – 153 (CLOT)
Snowden, J et al; Br J Haem 2011; 154; 76 – 103 (iMiDs)
Short, N and Connors, J; The Oncologist 2014; 19 (1): 82 – 93 (DOACs)
NICE guideline NG89, published March 2018
1 Raskob, G et al; NEJM 2018; 378: 615 – 624 (edoxaban)
2 Young, A et al; Select-D trial; presented at ASH 2017 (rivaroxaban)