Anticoagulation in active cancer: Special considerations

A LEO Pharma Symposium on the occasion of the:
23rd Congress of the European Association of Hospital Pharmacists 2018 (EAHP)
Symposium agenda

12:00 – 12:10
Introduction: Cancer Associated Thrombosis
Chair: Prof James O’Donnell, Haematologist, Ireland

12:10 – 12:30
Why anticoagulation in active cancer is complex
Prof James O’Donnell, Haematologist, Ireland

12:30 – 12:50
VTE in active cancer patients: The impact of drug interactions on chemotherapy
Dr Vincent Launay-Vacher, Pharmacist, France

12:50 – 13:10
Role of the pharmacist in cancer associated thrombosis management: How to improve patient care
Kieron Power, Pharmacist, UK

13:10 – 13:25
Discussion
All faculty

13:25 – 13:30
Conclusion
Introduction:
Cancer Associated Thrombosis

Prof. James O’Donnell
National Coagulation Centre, St James’s Hospital, Dublin
Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland
Cancer is associated with an increased risk of venous thrombosis

Risk of venous thrombosis in cancer (Multiple meta-analyses)

- **5-7 fold** increased risk cf age/sex matched controls\(^1\)

- 20% of all cancer patients develop clinical VTE disease\(^1\)

1) Petersen LJ. Cancer Treatment Reviews 2009.
Cancer is associated with an increased risk of venous thrombosis

Risk of venous thrombosis in cancer

- **5-7 fold** increased risk cf age/sex matched controls\(^1\)

- 20% of all cancer patients develop clinical VTE disease\(^1\)

- 50% asymptomatic DVT on screening\(^2\)

- 95% cancer patients have coagulation activation\(^3\)

---

1) Petersen LJ. Cancer Treatment Reviews 2009. 2) 3)
Cancer is associated with an increased risk of venous thrombosis

Risk of venous thrombosis in cancer

- **5-7 fold** increased risk cf age/sex matched controls\(^1\)
- 20% of all cancer patients develop clinical VTE disease\(^1\)
- 50% asymptomatic DVT on screening\(^2\)
- 95% cancer patients have coagulation activation\(^3\)

---

**Second commonest cause of death in cancer patients**\(^4\)

---

1) Petersen LJ. Cancer Treatment Reviews 2009.
Specific types of cancer are associated with higher risk of thrombosis

Adapted from Chew H. Arch Intern Med 2006

<table>
<thead>
<tr>
<th>Site</th>
<th>Standardised incidence ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>6</td>
</tr>
<tr>
<td>Ovary</td>
<td>5.2</td>
</tr>
<tr>
<td>Prostate</td>
<td>4.2</td>
</tr>
<tr>
<td>Lung</td>
<td>1.8</td>
</tr>
<tr>
<td>Colon / Rectum</td>
<td>1.6 / 0.7</td>
</tr>
</tbody>
</table>

Adapted from Sorensen HT. NEJM 1998
Adapted from Sorensen HT. NEJM 2000
Risk of cancer-associated thrombosis is further increased in patients with metastatic disease

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Local</th>
<th>Regional</th>
<th>Remote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>4.3</td>
<td>5.3</td>
<td>19.7</td>
</tr>
<tr>
<td>Stomach</td>
<td>2.7</td>
<td>3.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Lung</td>
<td>1.1</td>
<td>2.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.6</td>
<td>2.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Breast</td>
<td>0.6</td>
<td>1.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Adapted from Wun T. Best Practice&Research Clinical Haematology 2009
Cancer treatment further increases the risk of thrombosis

Chemotherapy\textsuperscript{1-5}
- Independent risk factor for thrombosis
- Overall risk increased 7-fold – varies with type of drugs
- Doxorubicin / Cisplatin / Thalidomide / Lenalidomide / Asparaginase

Surgery – especially major abdominal surgery\textsuperscript{6}

Hormonal therapy\textsuperscript{5,7,8}

Indwelling catheter\textsuperscript{9}

Immobility\textsuperscript{6}

VTE in cancer patients is associated with reduction in overall survival

Adapted from Sorensen HT. NEJM 2000
CAT – the scale of the clinical challenge?

England and Wales – APPTG 2016

• UK - VTE is second commonest cause of death in cancer patients

• Over 4000 cancer deaths per annum caused by CAT

• CAT-related deaths increasing year on year
  ✓ (Ageing population / longer cancer survival / novel therapies)

APPTG report: VTE in cancer 2016, available on apptg.org.uk:
What is happening in the real world?

England and Wales – APPTG report 2016

• VTE is second commonest cause of death in cancer patients

• Over 4000 cancer deaths per annum caused by CAT

• CAT-related deaths increasing year on year
  o Ageing population / longer cancer survival / novel therapies

Many of these deaths may be preventable

APPTG report: VTE in cancer 2016, available on apptg.org.uk:
Symposium agenda

12:00 – 12:10
Introduction: Cancer Associated Thrombosis
Chair: Prof James O’Donnell, Haematologist, Ireland

12:10 – 12:30
Why anticoagulation in active cancer is complex
Prof James O’Donnell, Haematologist, Ireland
Why anticoagulation in active cancer is complex

Prof. James O’Donnell
National Coagulation Centre, St James’s Hospital, Dublin
Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland
Overview

Brief introduction – key issues re thrombosis in cancer patients

Treatment of cancer-associated thrombosis
- Optimal anticoagulant
- Optimal duration of therapy

Common problems
- Recurrent episodes of VTE
- Thrombocytopenia
- Renal impairment
What is active cancer?

Active cancer defined by histological confirmation of malignancy and any of the following:

- Cancer diagnosis within the previous 6 months
- Recurrent, regionally advanced or metastatic disease
- Cancer for which treatment administered within 6 months
- Hematological malignancy not in complete remission
What is venous thrombosis?

Deep vein thrombosis (DVT)
- Pain and or swelling involving calf or whole leg
- Doppler ultrasound

Pulmonary embolism (PE)
- Short of breath / pleuritic chest pain / haemoptysis
- CTPA
Management of venous thrombosis in patients with active cancer

• More difficult than treatment of VTE in non-cancer patients

• Two major issues
Risk of recurrent thrombotic events during anticoagulant therapy is increased

Adapted from Prandoni O. Blood 2002
Risk of bleeding complications during anticoagulant therapy is increased

Adapted from Prandoni P. Blood 2002
What is the optimal treatment regimen for CAT?

Consider in two distinct parts:

- **Initial management** – (5 to 7 days)
  - UFH or LMWH

- **Ongoing treatment** – (3 to 6 months)
  - LMWH or Warfarin or DOAC
## Initial management of cancer-related VTE

### Consensus guidelines

<table>
<thead>
<tr>
<th></th>
<th>NCCN 2011</th>
<th>ASCO 2013</th>
<th>BCSH 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial / acute</td>
<td>LMWH</td>
<td>LMWH is preferred for initial 5-10 d of treatment in patients with CrCl &gt; 30ml/min.</td>
<td>Initial treatment should be with LMWH.</td>
</tr>
<tr>
<td>treatment</td>
<td>Dalteparin 200U/kg OD Enoxaparin 1mg/kg BID Tinzaparin 175U/kg OD APTT adjusted UFH infusion.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is the optimal treatment regimen for CAT?

Consider in two distinct parts:

• **Initial management** – (5 to 7 days)
  ◦ UFH or LMWH

• **Ongoing treatment** – (3 to 6 months)
  ◦ LMWH or Warfarin or DOAC
Warfarin therapy in cancer patients is difficult

Time in target therapeutic INR range is often poor

- Anorexia / malnutrition
- Vomiting
- Drug interactions
- Abnormal liver function
- Thrombocytopenia
- Surgical procedures
Oncology practise – LMWH versus warfarin

Advantages of LMWH
- No need for laboratory monitoring
- Shorter half-life facilitates temporary interruption (thrombocytopenia / procedures)
- Fewer interactions
- No food / dietary interactions

Disadvantages of LMWH
- Cost
- Daily subcutaneous injections
CLOT trial

*Comparison of LMWH versus OAC in cancer pts with VTE*

**Solid tumour and acute proximal DVT / PE**

- Breast; colorectal; lung; gynae; GUT; pancreas; other ($n = 676$)

**Dalteparin**
- 200IU/kg for 5-7 days

**Dalteparin**
- 200IU/kg for 4 weeks – then 150IU/kg

**Dalteparin**
- 200IU/kg for 5-7 days

**Oral coumarin**

---

Total 6 months

---

Multicentre, open-label randomised controlled trial
48 centres in 8 countries (6 countries – warfarin)

Adapted from Lee et al, NEJM 2003;349:146
Recurrent VTE was significantly reduced for cancer patients on LMWH versus coumarin

Adapted from Lee et al, NEJM 2003;349:146
Recurrent VTE was significantly reduced for cancer patients on LMWH versus coumarin

P=0.002

Coumarin (53 events; 17%)
- 20 events INR <2.0

Dalteparin (27 events; 9%)

One episode of symptomatic venous thrombosis prevented for every 13 cancer patients treated with LMWH

Adapted from Lee et al, NEJM 2003;349:146
LMWH versus warfarin for treatment of for VTE in cancer patients – CLOT study

No significant difference in risk of bleeding
(LMWH 6% versus coumarin 4%; P=0.27)

Lee et al, NEJM 2003;349:146
CATCH study

Comparison of Acute Treatments in Cancer Haemostasis

- Lee et al, JAMA - August 18, 2015;314:677

- A randomized trial of long-term Tinzaparin vs. warfarin for treatment of acute venous thromboembolism in cancer patients

- Global study with 164 centres in 32 countries

- Objectively confirmed symptomatic proximal DVT, PE or both
CATCH study design
Prospective, randomized open-label, with blinded endpoint - (similar to that in CLOT)

Inclusion Criteria
• 18 yr or older
• active cancer
• proximal DVT &/or PE

Tinzaparin 175 IU/kg once daily for 6 months
(Same full dose)

Initial Tinzaparin 175 IU/kg for 5–10 days
Followed by Warfarin (target INR 2 – 3)

• Follow-up clinic visits on days 7, 14, 30 and then every month
• Telephone contacts at 2 weeks after every monthly visit
• INR performed at least once every 2 weeks

Adapted from Lee et al, JAMA - August 18, 2015;314:677
Recurrent VTE was reduced for cancer patients on tinzaparin versus warfarin– CATCH Study

Adapted from Lee et al, JAMA - August 18, 2015;314:677

Cumulative risk of recurrent VTE (%) vs. Days post-randomization

- **Warfarin**
  - (45 events; 10.5%)
  - Wald test $P = .07$

- **Tinzaparin**
  - (31 events; 7.2%)
Bleedings - tinzaparin versus warfarin for treatment of for VTE in cancer patients – CATCH Study

Adapted from Lee et al, JAMA - August 18, 2015;314:677

HR 0.89 (95% CI 0.40–1.99)  
p = 0.77

Warfarin, 2.4%  
(11 events); TTR 47%

Tinzaparin, 2.7%  
(12 events)
# Long-term management of CAT

## Consensus guidelines

<table>
<thead>
<tr>
<th>Long term treatment</th>
<th>ACCP 2012</th>
<th>ASCO 2013</th>
<th>BCSH 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH preferred to VKA.</td>
<td>LMWH is preferred for long-term therapy.</td>
<td>Initial treatment should be with LMWH.</td>
<td></td>
</tr>
</tbody>
</table>
## Duration of anticoagulant therapy in CAT treatment

### Consensus guidelines

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>ACCP 2012</th>
<th>ASCO 2013</th>
<th>BCSH 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extended anticoagulant therapy is preferred to 3 months of treatment [2B].</td>
<td>At least 6 months duration.</td>
<td>Initial treatment should be with LMWH for 6 months, if tolerated.</td>
</tr>
</tbody>
</table>
Extended duration of anticoagulant therapy beyond 6 months?

No published studies address optimal anticoagulation beyond first 6 months in patients with cancer.

Should be considered for selected patients because of persistent high risk of recurrence in those with active cancer.
Treatment of cancer-associated thrombosis

- Optimal anticoagulant
- Optimal duration of therapy

Common clinical problems

- Recurrent episodes of VTE
- Thrombocytopenia
- Renal impairment
Treatment of recurrent VTE during anticoagulant therapy

Recurrent VTE - common clinical problem
- 6 - 9% of cancer VTE managed with LMWH
- 10 - 17% of cancer VTE managed with Warfarin

Limited evidence regarding optimal treatment
- If VTE on warfarin switch to therapeutic dose LMWH
Treatment of recurrent VTE during anticoagulant therapy

Recurrent VTE on LMWH

• Assess compliance
• Exclude HIT

LMWH dose escalation

If VTE on reduced dose of therapeutic LMWH

• 75% dose after first month in CLOT study
• Increase LMWH dose back to 100%
Treatment of recurrent VTE during anticoagulant therapy

If recurrent VTE whilst on full-dose therapeutic LMWH

- Increase dose by further 20-25% (Carrier et al, 2009)
- Effective in VTE prevention in 90% patients over > 3 months

- Tailor dose by measuring peak anti-Xa levels
- (BD regimen - peak 1.0 U/ml; OD regimen – peak 1-2 U/ml)
Treatment of recurrent VTE during anticoagulant therapy

- If recurrent VTE whilst on full-dose therapeutic LMWH
  - Increase dose by further 20-25% (Carrier et al, 2009)
  - Effective in VTE prevention in 90% patients over > 3 months

- Tailor dose by measuring peak anti-Xa levels
  - (BD regimen - peak 1.0 U/ml; OD regimen – peak 0.7 - 1.2 U/ml)
Treatment of VTE in cancer patients with thrombocytopenia

Thrombocytopenia is common in patients with cancer

If platelet count is maintained > 50 x 10^9/L

- Use therapeutic dose LMWH

Elalamy J. Throm Haemo 2017
Lee A. Blood 2013
Carrier M. J Thromb Haemost 2013
Treatment of VTE in cancer patients with thrombocytopenia

If platelet count < 50

**Platelet transfusion to maintain count > 50**
- Use therapeutic dose LMWH
- Especially in first month after acute VTE

If platelet count cannot be maintained > 50
- Platelet count 20 – 50: Half-dose LMWH
- Platelet count < 20: Hold anticoagulation

Consider retrievable IVC filter if within 1 month after VTE

Lee A. Blood 2013
Carrier M. J Thromb Haemost 2013
Treatment of VTE in cancer patients with renal impairment

Renal impairment is common in patients with cancer

- LMWH accumulation can occur
- Enoxaparin > tinzaparin

- Manufacturer-recommendations for enoxaparin

- Dose adjustments based upon anti-Xa monitoring
Treatment of VTE in cancer patients with renal impairment

• Renal impairment is common in patients with cancer

✓ Enoxaparin: In patients with severe renal impairment (creatinine clearance 15-30 mL/min), since exposure of enoxaparin sodium is significantly increased, a dosage adjustment is recommended for therapeutic and prophylactic dosage range (1)

✓ Tinzaparin: Evidence suggests no accumulation down to 20 ml/min, but consider anti Xa levels below 30 ml/min (2)

• Manufacturer-recommendations for enoxaparin

• Dose adjustments based upon anti-Xa monitoring
Edoxaban for the treatment of CAT
Hokusai study – Raskob et al, NEJM 2017

• Open label, non-inferiority trial
• 114 centres in 13 countries
• 1046 adult patients with confirmed proximal DVT or PE and active cancer

• Randomized:
  ✓ LMWH for at least 5 days followed by edoxaban 60mg OD
  ✓ LMWH dalteparin 200IU/kg OD for 1 month followed by dalteparin 150IU/kg OD.

• Treatment for at least 6 months and up to 12 months
Dalteparin versus Edoxaban - Recurrent VTE

Adapted from Hokusai study – Raskob et al, NEJM 2017
Dalteparin versus Edoxaban – major bleeding complications

Oral edoxaban was non-inferior (p=0.006) to subcutaneous dalteparin with respect to composite outcome of recurrent VTE or major bleeding

Adapted from Hokusai study – Raskob et al, NEJM 2017
Direct oral anticoagulants for CAT?

Outstanding questions to be addressed:

• Patients at high risk of bleeding - particularly GI bleeding
• Patients who develop bleeding complications
• Patients with significant renal or liver impairment
• Patients with thrombocytopenia
• Patients who develop recurrent CAT on anticoagulant therapy
• Patients on chemotherapy drugs that interfere with DOAC clearance
• No easy DOAC monitoring
Patients with active cancer are heterogeneous

Management of CAT in the real world is complex and different to RCT!

- Thrombocytopenia and renal impairment
- Liver impairment

- Bleeding complications - eg GIT bleeding / brain metastases
- Solid tumors versus hematological malignancy

- Nausea / vomiting / diarrhoea
- Extremes of weight
- Poor performance status
- Chemo pharmacokinetics
- Interruption for surgery / procedures
One size treatment for CAT does not fit all ...

Obvious differences for treatment of CAT in:

• Young woman with early stage breast cancer
• Elderly male with metastatic pancreatic cancer receiving palliative care
Personalized Medicine in CAT
CAT treatment tailored specifically for individual patient

- Guideline recommendations
- Type of tumour?
- Metastasis?
- Bleeding risk?
- Co-morbidities?
- Overall prognosis?
- Type of chemotherapy?
- Adjuvant therapies?
- Renal and liver function?
- Platelet count?
- Need for surgery/interventions?
- Economic considerations?

Patient preferences – empowered to be actively involved in decision making process
Patients need to be involved in treatment of CAT

Patient preference (Noble et al. Haematologica 2015)

• CAT patients asked to rank most important characteristics of anticoagulant therapy
  1. Does not interfere with cancer therapy
  2. Maximum efficacy for thrombosis treatment
  3. Bleeding risk minimized
  4. Only once these characteristics are met – prefer oral over subcutaneous
Multi-disciplinary team involvement is critical for optimal treatment of CAT

**Lack of ownership**

- Haematologists / Oncologists / Emergency care / Primary care
- Radiologists
- **Hospital and primary care pharmacists**
- Hospital and community nursing

**Inconsistent treatment and strategies**
Conclusions

Outlined the options for the treatment of cancer-related VTE

• LMWH for 6 months constitutes consensus treatment of choice
• LMWH dose escalation preferred option for recurrent VTE
• Await data from ongoing studies of DOACs for CAT

Management of VTE in patients with active cancer is complicated

• Critical need for personalized treatment regimes
• Multidisciplinary team approach and patient involvement
Thank you for listening
Symposium agenda

12:00 – 12:10
Introduction: Cancer Associated Thrombosis
Chair: Prof James O’Donnell, Haematologist, Ireland

12:10 – 12:30
Why anticoagulation in active cancer is complex
Prof. James O’Donnell, Haematologist, Ireland

12:30 – 12:50
VTE in active cancer patients: The impact of drug interactions on chemotherapy
Dr. Nicolas Janus, Pharmacist, France
VTE in active cancer patients: The impact of drug interactions on chemotherapy

Dr Nicolas Janus, PharmD
Global Medical Manager, Global Thrombosis Strategy, LEO Pharma A/S, Ballerup, Denmark

Former Clinical Pharmacist, Nephrology Dpt (Pr Deray), Pitié-Salpêtrière Hospital, Paris, France
Former Attached Practitioner in the Nephrology Dpt (Pr Deray) of the Pitié-Salpêtrière Hospital, Paris, France
Former member “Service ICAR”, Pitié-Salpêtrière Hospital, Paris, France (with Dr Launay-Vacher)
Former member of the EAHP Scientific Committee
Former President of the EFP (French member of the EAHP)

Disclosure (before 2017):
Bayer; Baxter; Boehringer-Ingelheim; B-Braun; Daichii Sankyo France; Fresenius Medical Care; Gilead; IPSEN; LEO Pharma; Pfizer; Pierre Fabre; Roche; Sanofi; Teva; ViiV; Vifor Pharma
Drug-Drug Interactions
What are we talking about?

Pharmacokinetic interactions

Efficacy risks: VTE
Because of the inhibition of the metabolism

Safety risks: Bleeding
Because of induction of metabolism

Pharmacodynamic interactions

Efficacy risks: VTE
Because of antagonist effects on the body

Safety risks: Bleeding
Because of synergic effects on the body
Pharmacokinetic Drug-Drug Interactions

What are we talking about?

- Substrates of the same CYP/Pgp
- CYP / Pgp’s inducers
- CYP / Pgp’s inhibitors
Polypharmacy and DDI in cancer
A great concern in cancer patients?

Polypharmacy is common in cancer patients

84.2% of cancer patients
With polypharmacy or excessive polypharmacy

Adapted from Nightingale G. J Clin Oncol 2015
Polypharmacy and DDI in cancer

What are the consequences of polymedication in cancer patients?

442 cancer patients aged > 70 years with chemotherapy
High prevalence of PDI in older cancer patients was reported with 87% of potential drug interaction between daily medications and 13% between a daily medications and a chemotherapy.

105 patients with advanced NSCLC, 100 patients with advanced ER-negative breast cancer (BC) and 100 hospice inpatients (HO) with advanced malignancies between 2010 and 2015.

Primary study objective was to assess the prognostic value of the severity of DDI

The severity of DDI was significantly associated with inferior overall survival in BC (HR=1.34, p=0.018), but not in NSCLC.

Polymedication is associated with a higher mortality in cancer patients

Adapted from Lambrecht Jorgensen T. ESMO 2017. Symposium
Drug-Drug Interactions

What are we talking about?

Adapted from Gundabolu K. J Oncol Pract 2017
Drug-Drug Interactions
CYP3A4 and P-Gp implication for oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct, reversible inhibition of Factor Xa</td>
<td>Direct, reversible inhibition of thrombin</td>
<td>Direct, reversible inhibition of Factor Xa</td>
<td>Direct, reversible inhibition of Factor Xa</td>
<td>Vitamin K antagonist</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80-100%*</td>
<td>6.8%</td>
<td>50%</td>
<td>60%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>92-95%</td>
<td>34-33%</td>
<td>3-4</td>
<td>1-3</td>
<td>4</td>
</tr>
<tr>
<td><strong>t_{max} (h)</strong></td>
<td>3-4</td>
<td>0.5-2</td>
<td>With t_{max}</td>
<td>With t_{max}</td>
<td>With t_{max}</td>
</tr>
<tr>
<td><strong>t_{1/2} (h)</strong></td>
<td>5-13</td>
<td>11-14</td>
<td>12</td>
<td>6-11</td>
<td>20-60</td>
</tr>
<tr>
<td><strong>Dosing for VTE treatment</strong></td>
<td>od (15 mg bid for 3 weeks, followed by 20 mg od maintenance)</td>
<td>bid (two 75 mg capsules bid)</td>
<td>bid (10 mg bid for 7 days, followed by 5 mg bid maintenance)</td>
<td>od (two 30 mg capsules od)</td>
<td>Started alongside parenteral anticoagulant, which is discontinued when the INR reaches 2.0; warfarin dose is then adjusted to maintain INR 2.0-3.0. Negligible</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>-66% (-33% undergoes renal metabolism and 33% excreted as unchanged drug)</td>
<td>85%</td>
<td>-27%</td>
<td>-35%</td>
<td>Negligible</td>
</tr>
<tr>
<td><strong>Elimination pathway</strong></td>
<td>CYP3A4 metabolism, P-gp transport</td>
<td>Esterase-mediated hydrolysis, P-gp transport</td>
<td>CYP3A4 metabolism, P-gp transport</td>
<td>P-gp transport</td>
<td>CYP60 enzymes including CYP2C9, 2C19, 2C8, 2C18, 162, 3A4</td>
</tr>
</tbody>
</table>

* Bioavailability of rivaroxaban calculated for 10 mg dose.

P-gp and CYP are not involved in the metabolism of LMWHs

Adapted from Bauersachs R. Euro J Int Med 2014
DDI with oral anticoagulation

Increased bleeding events

Records of patients prescribed rivaroxaban over a 5 year period with at least one concomitant medication of interest (n=747).

The authors investigated the effect of other drugs (inhibitors) on Rivaroxaban safety.

No investigation of the potential effect of other drugs (inducers) on Rivaroxaban efficacy.

No investigation on the potential effects of Rivaroxaban on other drugs.

Adapted from Momin W. ESC Congress 2017. Abstract 5742
DDI with oral anticoagulation

Increased bleeding events

Adapted from Momin W. ESC Congress 2017. Abstract 5742
DDI with oral anticoagulation

Increased bleeding events

“Concomitant use of either CYP3A4 or Pgp inhibitors with rivaroxaban was associated with increased bleeding risk. CYP3A4 inhibitors were associated with the greatest risk, while Pgp inhibitors were associated with an increased risk similar to that seen for patients prescribed NSAIDs or PAIs.”

“Our data is limited by the number of patients available for analysis and use of ICD codes to determine bleeding. However, our study provides evidence that coadministration of rivaroxaban with either CYP3A4 or Pgp inhibitors may be associated with an increased risk of bleeding.”

Adapted from Momin W. ESC Congress 2017. Abstract 5742
DDI with oral anticoagulants

Increasing PK parameters with verapamil*

Impact of DDI (+/- mild RI) on the half life (h) of rivaroxaban

Day 1
Without Verapamil
Normal Renal Function

Day 15
With Verapamil
Normal Renal Function

Day 1
Without Verapamil
Mild Renal Insufficiency

Day 15
With Verapamil
Mild Renal Insufficiency

p-value < 0.05

8.4h

9.9h

10.4h

14.9h

Adapted from Greenblat DJ. J Clin Pharmacol 2017; *Verapamil is a P-gp and moderate CYP3A inhibitor
DDI with oral anticoagulants
Increasing PK parameters with verapamil*

Impact of DDI (± mild RI) on the AUC (ng.h/mL) of rivaroxaban

Day 1
Without Verapamil
Normal Renal Function

Day 15
With Verapamil
Normal Renal Function

Day 1
Without Verapamil
Mild Renal Insufficiency

Day 15
With Verapamil
Mild Renal Insufficiency

p-value < 0.001

Adapted from Greenblat DJ. J Clin Pharmacol 2017; *Verapamil is a P-gp and moderate CYP3A inhibitor
DDI with oral anticoagulant drugs

Many case reports in non CAT patients and a few in CAT patients: 2 examples

“Conversely, heparins are not subject to drug-drug interactions and, therefore, can be safely co-administered with antiretroviral agents”

Adapted From Lakatos B. Swiss Medical Weekly 2014.

“DOACs have many important drug interactions which need to be considered prior to prescribing”

“Awareness of these drug interactions amongst clinicians is variable”

Adapted from Burden T. Clinical Med 2018
DDI with oral anticoagulant drugs
Many case reports with many different drugs

Table 2. Interactions between selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine-reuptake inhibitors (SNRIs), and NOACs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
<th>Cases ≥75 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>CR [12]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Citalopram</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>CR [12]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>

Published DDI with DOACs:
- Paroxetine
- Sertraline
- Fluvastatin
- Metronidazole
- Carbamazepin
- Nevirapine
- Rifampicin
- Clarithromycin
- Amiodarone
- Diltiazem
- Erythromycin
- Fluconazole
- Ketoconazole
- Ritonavir
- Saw Palmetto
- Verapamil
- Oxcarbazepine
- Aliskiren
- Atorvastatin
- Ciclosporin
- Simavastin
- Tacrolimus
- Bisoprolol

DDI with anticoagulant in CAT patients

What do we now?

Adapted from Short N. The Oncologist 2014

Many anticancer drugs and many supportive care drugs are metabolised by CYP3A4 and/or P-Gp.
Food-Drug Interactions

Do we need to be concern? What do we know?

Many natural substance could be inhibitor of CYP3A4

Adapted from Di Minno A. Blood 2017.
Conclusion

• Optimal management in cancer patients include to consider DDI/FDI interactions.

• Both LMWHs and DOACs are exposed to PD DDI

• Oral anticoagulants are more potentially exposed to PK and PD DDI

• Anticoagulants are not exposed to FDI, but:
  ▪ Check for meals intake
  ▪ Check for natural substances

Cancer patients are special

There is a need for specific considerations

One does not fit all
Thank you for listening
Symposium agenda

12:00 – 12:10
Introduction: Cancer Associated Thrombosis
Chair: Prof James O’Donnell, Haematologist, Ireland

12:10 – 12:30
Why anticoagulation in active cancer is complex
Prof James O’Donnell, Haematologist, Ireland

12:30 – 12:50
VTE in active cancer patients: The impact of drug interactions on chemotherapy
Dr Nicolas Janus, Pharmacist, France

12:50 – 13:10
Role of the pharmacist in cancer associated thrombosis management: How to improve patient care
Kieron Power, Pharmacist, UK
The Role of The Pharmacist in Cancer Associated Thrombosis Management:

How to Improve Patient Care

Kieron Power

VTE Clinic Pharmacist at Singleton Hospital, ABMU Health Board, Swansea, Wales

A LEO Pharma Symposium on the occasion of the 23rd Congress of the European Association of Hospital Pharmacists 2018
Contents

• Is CAT relevant to pharmacists?
• What is the role of pharmacy?
• How do we increase adherence?
• How do we minimise the burden of disease?
Is CAT relevant to pharmacists?

Take Home Message 1

One in five cancer patients develop blood clots which could be fatal

Awareness are cancer-associated thrombosis is low, say campaigners

At Singleton (own data):
In a six month period between June 2017 and January 2018:

36 patients of 156 cancer patients (23%) were CAT patients

Source Wales Online, May 2017
Is CAT relevant to pharmacists? (2)

Take Home Message 1

• Second most common cause of death in cancer patients (after the tumour itself)

• Affects survival rate (12% one year survival rate for CAT patients vs 36% in control patients, Sorensen et al 2000)

• Cancer is one of the most important risk factor for VTE in institutionalized patients (Heit JA et al 2002)

• Risk further increased by chemotherapy (Haddad et al 2006)
Is CAT relevant to pharmacists? (3)

Take Home Message 2

• The PELICAN study (Noble et al. 2015) focused on patient understanding and anxieties in CAT patients

• Focused on patients who:
  ◦ Had cancer, but not had CAT (pre-diagnosis)
  ◦ Had cancer and had been diagnosed with CAT (post-diagnosis)

• Consistent findings across patients interviewed

• Lack of understanding/awareness of CAT found in both pre- and post-diagnosis arm

• High anxiety levels found in post diagnosis arm
Is CAT relevant to pharmacists? (4)
The PELICAN Study (Noble et al 2015)

• Example of findings:
  ◦ Patients more likely to associate clots to flying than cancer
  ◦ People who developed CAT were more likely to attribute symptoms to chemotherapy
  ◦ Clinicians often mistook the symptoms for other conditions e.g. LRTI
  ◦ Post diagnosis, patients associated CAT with a worse prognosis for their disease
  ◦ Patients found the diagnostic process rushed
  ◦ Patients did not feel that they were given enough information about the diagnosis or treatment
  ◦ Patients would turn to the internet to gather information on their own, and learning about a potentially fatal condition, without access to support to answer their questions
  ◦ Patients compared the information given with regards to neutropenic sepsis v CAT
Is CAT relevant to pharmacists? (5)

Take Home Message 3

• Pharmacists interact with cancer patients in numerous sectors and locations
Is CAT relevant to pharmacists? (6)

What we know

- 1 in 5 cancer patients develop CAT
- Most patients with cancer have no awareness of the risks of developing CAT
- Once diagnosed, patients feel that they are not adequately counselled on the condition
- However..........

- Pharmacists regularly interact with cancer patients and could play a vital role in the management of CAT

Lyman GH. Cancer 2011; Farge. Thromb Res 2010
The Role of The Pharmacist
Pre vs Post CAT Diagnosis

Pre-Diagnosis
• Raising Awareness of CAT
• Risk Assessment
• Thromboprophylaxis

Post-Diagnosis
• Counselling
• Prescribing (Not all Europe)
• Supply
• Monitoring
• Review
Pre-Diagnosis
Risks of lack of awareness

• Improved awareness of CAT needed
  ◦ Amongst patients
  ◦ Amongst healthcare professionals

• Lack of awareness delays patients accessing medical assessment

• Delays can increase short and long term complications e.g.
  ◦ Post-Thrombotic Syndrome
  ◦ Complications of PE (e.g. RV Strain, pulmonary hypertension)
  ◦ Re-occurrence
  ◦ Serious or fatal PE

Source: BloodJournal
Raising Awareness

Patients

- Oncology clinics
  - Highlight risk of CAT when prescribing medication
- Supply of medication
  - Discuss risks of CAT whilst counselling patient on medication
- Admission to hospital
  - Ensure admitted cancer patients risk assessed for thromboprophylaxis
- Guidelines
  - Routine thromboprophylaxis not currently recommended in ambulatory patients (ESMO 2011)
  - May be considered in patients with high risk cancers and/or high risk treatments (e.g. Thalidomide in myeloma (ESMO 2011)
  - Pharmacists can play a key role in developing guidelines and risk assessment
Raising Awareness (2)
Health Care Professionals

• PELICAN study also highlighted lack of awareness amongst HCP’s (Noble S et al 2015)
• Previously described methods not likely to be undertaken without HCP education
• Many HCP’s interact with cancer patients
• Pharmacy can lead on awareness campaigns
  ◦ Meetings
  ◦ Education sessions

Source: SmartMeetings
Raising Awareness (3)

- Integrated into clinical practice
- Counselling
- Leaflets
- Posters
- Websites
- Videos/Video Cards
- Support Groups
Post Diagnosis
Lack of support and education

- PELICAN study (Noble S et al 2015) highlighted:
  - High level of anxiety post diagnosis that patients felt not adequately addressed
  - Lack of education around treatment

- Pharmacists can play an important role:
  - Counselling patients on the correct use of medication
  - Managing expectation around treatment aims and outcomes
  - Acting as a point of contact for queries and concerns
  - Supporting patients to achieve compliance with therapy
  - Empower patients to take ownership of their own condition
  - Ensuring most effective therapies used (treatment guideline development)
Post Diagnosis

Work undertaken at Singleton Hospital (Personal Data)

Findings at Singleton Hospital

- Diagnostic pathways varied (up to 8 pathways identified creating variation in practice and patient experience)
- ~80% of patients have doses adjusted to reflect changes in body weight
- ~70% of patients adequately monitored (U+E, FBC)
- ~60% of patients received at least minimum duration of therapy (6 months)
Post Diagnosis
Pharmacy-led CAT Clinic

• Summer 2017- Pharmacy CAT clinic developed and launched
• All CAT diagnosed referred to pharmacy clinic
• In most cases, same day appointments available
• Patients referred as:
  ◦ Symptomatic VTE’s (60%)
    — Referred via Admissions units and wards
  ◦ Incidental VTE’s (40%)
    — Referred via diagnostic sectors (e.g. radiology)
CAT Clinic
Pharmacists role

Ensure correct treatment prescribed

Clinically assess suitability of medication for patient:
- Clinical assessment
- Cautions and contraindications
- Interactions

Ensure supply of medication

Ensure follow up strategy developed

Ensure patient educated and empowered
- Administration
- Adverse drug effects
First Clinic Consultation
Patient Education and Empowerment

• Focused on patient education and reassurance

- Explanation of CAT and the link between cancer and thrombosis
- Explanation of how CAT will be treated and what expectations the patient can have
- Each of these has a degree of anxiety for the patient
- A standard clinic appointment slot is generally not enough to adequately address these issues
First Clinic Consultation
Patient Education and Empowerment

1. Administration
2. Side effects
3. Drug-drug/Food-Drug Interactions
4. Monitoring
5. Collection of waste
6. Follow up
7. Supply
Specific Issues
Administration

• There is often a fear around the concept of self injecting, with patients often associating the term “injection” with intravenous products.

• Studies focussing on other medications (Mohr et al 2002) have found self-administration strategies to achieve better rates of compliance than cases whereby a family member or district nurse administered the medication.

• Factors affecting compliance with injectable medication include (Brod et al 2008):
  ◦ Knowledge and understanding of treatment
  ◦ Patient training resources
  ◦ Efficacy and side effects

• Patients prefer the empowerment and freedom of self-administration (Noble et al 2015)
Patient Education

Administration

• Where possible we encourage self-administration. This is achieved by

  **In consultation, practical demonstrations:**
  The first intervention in terms of attempting to achieve self-administration. Patient is shown how and given the opportunity to self-administer with support from clinic staff.

  Patients usually respond well to this type of support and in most cases feel that any anxieties they have around self-injection are alleviated

  **Further support:**
  Patients may have further questions about administration after the consultation. We utilise other methods of re-enforcing counselling points such as booklets
Patient Education

Administration

• Good technique vital!!
  ◦ Bruising one of the main reasons for poor compliance
  ◦ Good technique reduces incidence of bruising
Specific Issues

Adverse Drug Reactions (ADRs)

• Studies looking at self-administration of LMWH have largely focused on extended thromboprophylaxis strategies (Karlinski et al 2006, Baba et al 2015)
  ◦ Patient education around expectation of what side effects they are likely to have and how to address them is vital in both patients self-administering and those who are having the drug administered by others
• In a number of these cases ADRs have been reported as a factor in non-compliance (Karlinski et al 2006)
• It can also be a further source of anxiety to the patient
Patient Education
Adverse Drug Reactions (ADRs)

• *In consultation counselling*: Although the patient is counselled on side effects during the clinic consultation, there is a considerable amount of information given to the patient. Information on potentially serious side effects is prioritised, meaning that the patient is less likely to focus on minor ADRs
• Focusing on serious side effects during the consultation, with no focus on therapeutic benefits can be detrimental to patient compliance (Dyck et al 2005)
• Patient anxiety after the consultation may therefore increase, especially when minor side effects such as mild bruising occur
Patient Empowerment

- Most clinic appointments 20-30mins
- Difficult to achieve all previously described roles within time frame
- Considerable amount of information
- Patient in best frame of mind?
- Clinic consultation model developed to prioritise information on a session by session basis
- Focus moved to “outside clinic support”
Patient Empowerment
Further strategies to re-enforce key points

- **Booklets**: Booklets illustrating the administration process in a step by step method are effective in allowing patients to re-enforce and review what was shown in clinic. They also provide practical guidance on dealing with such as things as minor side effects (e.g. bruising)
Patient Empowerment

- **Video cards:** We have utilised video cards, which show an in depth video on administration of the drug. Patients have responded very positively to this and seem to prefer the video to booklets. We currently utilise the video before showing the practical demonstration.
Patient Empowerment

- **Websites:** We have found websites to be the best method of patient education as patients are able to access a variety of information and interactive content, when they require. The CancerClot™ website is a resource that we look forward to sharing with our patients.
Other Issues
Other questions or concerns that the patient may have outside of the consultation include:

Supply:
Where will my next supply come from?

Interactions
• How does this interfere with my chemotherapy?
• What other medication can I take?

Monitoring:
• What plan is there to follow me up?
• I was told that this was serious, will I get re-scanned?
Wider Pharmacy Team

- Pharmacist role changing
- Technician role expanding to support this

In ABMU, CAT technician role created

- After 1 month in CAT clinic, patient referred to CAT technician “Virtual clinic”

Support with:

- Ongoing supply of medication
- Monitoring
- Recording weight
- Patient education and support
- Referral for review at 6 month point
The Six Month Question

- Treatment guidelines recommend 6 months of therapy
- Beyond that point, evidence and guidelines more difficult to interpret
- Scoring systems developed, e.g. OTTOWA (Louzada et al 2012) score, but not validated

Guidelines (BCSH 2015, ASCO 2013, NICE 2012, ESMO 2011) generally advise continuing anticoagulation if:
  - Active cancer and/or
  - Metastatic disease/chemotherapy

Pharmacists can play a role in:
  - Reviewing patients at 6 month point and deciding if anticoagulation to continue
  - Discussing with patient which agent to use, e.g. LMWH vs DOAC
How effective is pharmacy in the management of CAT

• Problems highlighted by PELICAN study (Noble S et al 2015)
• Potential answer lies with pharmacy?
• Study currently being undertaken
• Focus on both patient anxieties and knowledge retention
• Three arms
  ◦ Patients diagnosed and managed via previous pathways
  ◦ Patients diagnosed and managed by pharmacist-led CAT service
  ◦ Patients diagnosed and managed by pharmacist-led CAT service and given access to cancer clot
• Further potential to assess use of CancerClot as both a pre- and post-diagnostic educational tool
Summary

• CAT a serious and unpublicised condition
• CAT has a considerable physical and psychological impact on patients

Therefore:
- CAT **IS relevant** to pharmacists
- Pharmacy **DOES have a role** in the management of CAT
- Pharmacy **CAN increase adherence**
- Pharmacy **CAN minimise the burden** of disease
Thank you for listening
Symposium agenda

12:00 – 12:10
Introduction: Cancer Associated Thrombosis
Chair: Prof James O’Donnell, Haematologist, Ireland

12:10 – 12:30
Why anticoagulation in active cancer is complex
Prof James O’Donnell, Haematologist, Ireland

12:30 – 12:50
VTE in active cancer patients: The impact of drug interactions on chemotherapy
Dr Vincent Launay-Vacher, Pharmacist, France

12:50 – 13:10
Role of the pharmacist in cancer associated thrombosis management: How to improve patient care
Kieron Power, Pharmacist, UK

13:10 – 13:25
Discussion
All faculty

13:25 – 13:30
Conclusion
Thank you for listening