Recent advances in the management of thrombotic complications associated with cancer

Cándido E. Rivera, MD
Assistant Professor of Medicine
Mayo Clinic Jacksonville, Florida
Learning objectives

Discuss indications for anticoagulation prophylaxis in cancer patients

Discuss role of direct oral anticoagulants and low-molecular weight heparin in treatment of cancer associated venous thromboembolism
Cancer and thrombosis

The problem

• The reported incidence of cancer associated venous thrombosis varies widely between studies (1.6% to 6%)
• 4-7 x higher risk of Venous Thromboembolism (VTE)
• 3 x higher risk of recurrent VTE
• 2 x higher risk of bleeding with anticoagulation
• Thromboembolism is a leading cause of death for patients with malignancy

Mechanisms of thrombosis in cancer

What causes the problem

Extracellular vesicles may contain Tissue Factor

Neutrophil extracellular traps

Inflammatory cytokines - TNFα, IL-1β, IL-6, VEGF

Extracellular microRNAs

PAI-1

Risk factors

Cancer type (highest risk pancreatic, brain, stomach, lung) and cancer genetics (e.g. Jak2 V617F mutation)

Cancer stage (risk higher in advanced stages) and grade

Type of treatment (e.g. lenalidomide, asparaginase)

Underlying comorbidities including prior history of venous thromboembolism, thrombophilia carrier
The Khorana risk score

Who will develop chemotherapy associated venous thromboembolism?

Association of venous thromboembolism with multiple variables was characterized in:

Derivation cohort consisted of 2701 cancer outpatient from a prospective observational study

Risk model derived and validated in an independent cohort of 1365 patients from the same study

The Khorana risk score
Who will develop chemotherapy associated venous thromboembolism?

<table>
<thead>
<tr>
<th>Patient’s Characteristics</th>
<th>Risk score</th>
<th>Risk of short-term VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
<td>0 = low risk 0.3-0.8%</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gyn, GU)</td>
<td>1</td>
<td>1-2= intermediate risk 1.8-2.0%</td>
</tr>
<tr>
<td>Prechemotherapy platelet count ≥ 350 x10^9/L</td>
<td>1</td>
<td>&gt;2 = high risk 6.7-7.1%</td>
</tr>
<tr>
<td>Prechemotherapy Hgb &lt; 10 g/dL or use of Red Cell growth factors</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pre-chemo WBC count &gt;11 x10^9/L</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 35 kg/m2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Other Prediction Models for Venous thromboembolism in Cancer Patients

• **Protecht score** = Khorana + chemotherapeutic agents (cisplatin, carboplatin and gemcitabine)

• **Vienna Cancer and Thrombosis Study (CATS) score** = Khorana + d-dimer and soluble P-selectin

• **New Austrian prediction model** = based on tumor-site category and d-dimer biomarker


American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

Gary H. Lyman,¹,²,* Marc Carrier,³,* Cihan Ay,⁴ Marcello Di Nisio,⁵ Lisa K. Hicks,⁶ Alok A. Khorana,⁷ Andrew D. Leavitt,⁸,* Agnes Y. Y. Lee,¹⁰,¹¹ Fergus Macbeth,¹² Rebecca L. Morgan,¹³ Simon Noble,¹⁴ Elizabeth A. Sexton,¹⁵ David Stenehjem,¹⁶ Wojtek Wiercioch,¹³ Lara A. Kahale,¹⁷,* and Pablo Alonso-Coello¹⁸,*

¹Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA; ²Department of Medicine, University of Washington School of Medicine, Seattle, WA; ³Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada; ⁴Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria; ⁵Department of Medicine and Aging Sciences, University G. D’Annunzio, Chieti, Italy; ⁶Division of Hematology/Oncology, Department of Medicine, St. Michael’s Hospital, University of Toronto, Toronto, ON, Canada; ⁷Cleveland Clinic and Case Comprehensive Cancer Center, Cleveland, OH; ⁸Department of Laboratory Medicine and ⁹Division of Hematology/Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA; ¹⁰Division of Hematology, Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada; ¹¹Division of Medical Oncology, BC Cancer, Vancouver site, Provincial Health Services Authority, Vancouver, BC, Canada; ¹²Bristol, United Kingdom; ¹³Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; ¹⁴Division of Population Medicine, Cardiff University School of Medicine, Cardiff, United Kingdom; ¹⁵Salt Lake City, UT; ¹⁶College of Pharmacy, University of Minnesota, Duluth, MN; ¹⁷American University of Beirut (AUB) Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Center, American University of Beirut, Beirut, Lebanon; and ¹⁸Cochrane Iberoamérica, Biomedical Research Institute Sant Pau–CIBERESP, Barcelona, Spain

Thrombosis Prophylaxis Recommendations in Hospitalized Cancer patients

• For **hospitalized medical** patients with cancer:
  Use thromboprophylaxis during hospitalization
  LWWH over UFH
  Pharmacological prophylaxis over mechanical prophylaxis

• For **patients with cancer undergoing surgery**:
  In pts with low bleeding risk – pharmacologic prophylaxis
  In pts with high bleeding risk – mechanical prophylaxis
  In pts with high thrombosis risk but without high bleeding risk – both mechanical and pharmacologic prophylaxis

## Prevention of clots in ambulatory cancer patients

**Cassini trial**  
Xarelto 10 mg daily vs placebo  
VTE rates  
Xarelto 6% vs 8.8% placebo  
Major bleeding rates  
Xarelto 2% vs 1% placebo

Prevention of clots in ambulatory cancer patients

Avert trial

VTE rates
Apixaban 4.2% vs 10.2% placebo

Major bleeding rates
Apixaban 3.5% vs 1.8% placebo

Thromboprophylaxis in ambulatory cancer patients

No thromboprophylaxis in low-risk patients

Thromboprophylaxis in high-risk patients

ASH suggests
ISTH suggests
ASCO may be offered
NCCN consider


Treatment of cancer-associated Venous thromboembolism

It used to be low-molecular weight heparin...

**CLOT trial**
- Recurrent VTE: 15.7 % warfarin vs 7.9 % dalteparin
- Major Bleeding: 6% warfarin vs 4% dalteparin

**CATCH trial**
- Recurrent VTE: 10% warfarin vs 6.9% tinzaparin
- Major Bleeding: 2.7% warfarin vs 2.4% tinzaparin


Direct oral Anticoagulants in the management of cancer patients with venous thromboembolism

Edoxaban

Recurrent VTE:  
7.9% edoxaban vs 11.3% dalteparin

Major bleeding:  
6.9% edoxaban group vs 4.0 % dalteparin group

Direct oral Anticoagulants in the management of cancer patients with venous thromboembolism

Rivaroxaban

Recurrent VTE: 4% rivaroxaban vs 11% dalteparin

Major bleeding: 6% rivaroxaban vs 4% dalteparin

Young AM, et. al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D).

Direct oral Anticoagulants in the management of cancer patients with venous thromboembolism

Apixaban

Recurrent VTE: 5.6% apixaban vs 7.9 % dalteparin
Major bleeding: 3.8% apixaban vs 4.0% dalteparin

Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism

Consecutive patients treated with apixaban, rivaroxaban, or enoxaparin at Mayo Thrombophilia Clinic (March 1, 2013 to January 31, 2018)

There were 750 patients treated for acute Ca-VTE with apixaban (n = 224), rivaroxaban (n = 163), and enoxaparin (n = 363) within 14 days of diagnosis and for at least 3 months, or until study event.

Recurrence of VTE and major bleeding were similar in apixaban, rivaroxaban, and enoxaparin groups. Rivaroxaban was associated with higher CRNMB but lower mortality compared to apixaban and enoxaparin.

Treatment of cancer-associated Venous thromboembolism

- **Initial treatment**: 1st week
- **Primary Treatment**: 3-6 months
- **Long term treatment**: beyond 6 months
Treatment of cancer-associated Venous thromboembolism

Initial treatment
1st week

Primary Treatment 3-6 months
Long term treatment beyond 6 months
Initial treatment in patients with cancer diagnosed with venous thromboembolism

- Direct oral anticoagulant such as Apixaban, Edoxaban or Xarelto or LMWH
- LMWH favored over unfractionated heparin (except in severe renal failure)
- Caution with DOACs in patients with gastrointestinal cancers

Treatment of cancer-associated Venous thromboembolism

- Initial treatment: 1st week
- Primary Treatment: 3-6 months
- Long term treatment: beyond 6 months
Short and long-term treatment of cancer associated venous thromboembolism

• Direct oral anticoagulant such as Apixaban, Edoxaban or Rivaroxaban is preferred over LMWH

• Continue treatment beyond 6 months in patients with active cancer

Treatment of cancer-associated Venous thromboembolism

- Initial treatment: 1st week
- Primary Treatment: 3-6 months
- Long term treatment: beyond 6 months
Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism

Patients with acute venous thromboembolism (VTE) enrolled between 03/01/2013 and 04/30/2021 were followed prospectively to assess VTE recurrence, major bleeding (MB), clinically relevant non-major bleeding (CRNMB), and death

patients with Ca-VTE n=1702 (45.3 %) patients without VTE without cancer (n=2057)
gastrointestinal (n = 340)
pancreatic (n = 223)
hematologic (n = 188)
genitourinary (n = 163)
lung (n = 139), ovarian (n = 109,
breast (n = 97), renal (n = 75)
prostate (n = 73)
hepatobiliary (n = 70)
brain (n = 57)
other cancers (n = 168)

Wysokinski WE, et. al.
Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.
Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism

Wysokinski WE, Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.
Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism

Wysokinski WE, Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.
Influence of primary cancer site on clinical outcomes of anticoagulation for associated venous thromboembolism

Patients with hepatobiliary, pancreatic, genitourinary, and hematologic cancers had higher VTE recurrence rates, while major bleeding rates were not statistically different compared to patients without cancer.

Renal cancer patients, on the other hand, had a much higher rate of major bleeding but a similar VTE recurrence rate compared to non-cancer-VTE patients.

The lung, ovarian, gastrointestinal, breast, and prostate cancer groups showed VTE recurrence and MB rates that were not different from those of non-cancer-VTE.

A higher proportion of major bleeding versus VTE recurrence was observed in patients with renal, lung, hepatobiliary, gastrointestinal, ovarian, prostate, and “other cancers”, while patients with pancreatic, hematologic, genitourinary, and breast cancers had proportionally higher VTE recurrence than major bleeding.

These findings raise the possibility that modification of anticoagulation intensity and duration relative to specific cancer location may positively influence outcomes.

Wysokinski WE, Thromb Res. 2023 Jan;221:37-44 PMID: 36463701.
Direct oral anticoagulants compared with vitamin K inhibitor for stroke prevention in A-fib

Intracranial hemorrhage and gastrointestinal bleeding comparison

What about dose intensity of long-term anticoagulation in cancer patients with venous thromboembolism?

Reduced or low-dose direct oral anticoagulants have been studied in randomized controlled trials for the extended prevention of venous thromboembolism after 6 months of treatment at full, therapeutic doses
Apixaban for extended treatment of venous thromboembolism

After 6 months of therapeutic anticoagulation patients were randomized to:

- Continue full-dose therapeutic apixaban 5 mg orally twice daily
- Continue prophylactic dose apixaban 2.5 mg orally twice daily
- Placebo


Symptomatic recurrent VTE or VTE-related death

Major or clinically relevant nonmajor bleeding
**Exclusion Medical History and Concurrent Diseases**

a) Subjects with a provoked index event without the existence of a persistent risk factor for recurrence as described in the eligibility checklist.

b) More than 12 months of anticoagulation planned for the most recent DVT or PE (index event).

c) Subjects with indications for long-term treatment with a VKA, such as:
   - Mechanical valve
   - Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism
   - Multiple episodes of unprovoked DVT or PE

d) Subjects with cancer who will be treated indefinitely with anticoagulation therapy.

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

After 6 months of therapeutic anticoagulation patients were randomized to:

- Continue full-dose therapeutic rivaroxaban 20 mg orally daily
- Continue maintenance dose rivaroxaban 10 mg orally daily
- Discontinue rivaroxaban and start baby aspirin orally daily

Fatal or nonfatal venous thromboembolism

Major bleeding


Active cancer patients between 2-3% on each arm
Extended full dose versus low-dose direct oral anticoagulants (DOAC) in cancer patients.

Consecutive patients with VTE were identified using the Mayo Clinic VTE registry from March 1, 2013 to December 31, 2021.

148 patients (115 (78%) on apixaban and 33(22%) on rivaroxaban) were identified in the low dose DOAC and 3060 patients in the full-dose anticoagulation group.

Low-dose DOAC prescription was more likely in patients with pulmonary embolism alone or in combination with DVT.

Patients transitioned to low-dose DOAC had similar age, sex and weight compared to the full dose anticoagulation group.

The mean time to start of a low-dose DOAC was 5.4 months.

Vlazny DT, et. al. Poster #1276 presented at American Society of Hematology meeting December 2023
Extended full dose versus low-dose direct oral anticoagulants (DOAC) in cancer patients.

There was no significant difference in venous thromboembolism recurrence or death on different DOAC doses.

Apixaban continue to be the dominant DOAC used in the low-dose group

Most cancer patients on low-dose DOAC had lymphoma, prostate, melanoma, ovarian or breast cancer.

Vlazny DT, et. al. Poster #1276 presented at American Society of Hematology meeting December 2023
Additional considerations in the treatment of cancer associated venous thromboembolism

• In patients with cancer should you treat with anticoagulation:
  - Incidental PE   YES
  - Subsegmental PE YES
  - Visceral/splanchnic vein thrombosis YES though observation is also an option

For patients with cancer and recurrent VTE despite receiving therapeutic LMWH consider increasing the LMWH dose to a supratherapeutic level

• IVC filter is not recommended for prevention in recurrent VTE

Additional considerations in the treatment of cancer associated venous thromboembolism

Should you keep central venous catheter (CVC) in patients with cancer and CVC-related clot? YES

Continue therapeutic anticoagulation while the central venous catheter is in place.

Continue therapeutic anticoagulation for 3 months after central venous catheter is removed.

Consider thrombectomy/thrombolysis in patients with limb-threatening thrombosis and low risk of bleeding


Managing anticoagulation in thrombocytopenic patients with malignancy

Cut off plt count 50k/uL for therapeutic anticoagulation

Consider intermediate or prophylactic anticoagulation with plt count 20-50 k/uL

Consider timing of acute clot (< 3 months vs >3 months), type of tumor and treatment
Managing anticoagulation in thrombocytopenic patients with malignancy

Diagnosis of acute VTE in thrombocytopenic cancer patient

Is Plt < 50,000/μL?

Yes

Can patient receive platelet transfusions?

Standard-dose DOAC or weight-based full-dose LMWH

No

Is there a high-risk of clot propagation?

Yes

Consider observation without anticoagulation

No

Which anticoagulant is being used/planned?

LMWH

Plt 20,000-50,000/μL: Consider low or intermediate-dose LMWH; Plt < 20,000/μL: Hold Anticoagulation

Edoxaban

Plt 30,000-50,000/μL: Consider standard-dose edoxaban

Rivaroxaban

Plt 25,000-50,000/μL: Consider reduced-dose rivaroxaban OR hold anticoagulation

Apixaban

No studies or guidelines published yet

Can consider following Caravaggio protocol (hold anticoagulation for Plt < 50,000/μL)
Anticoagulant/cancer therapy drug to drug interactions

<table>
<thead>
<tr>
<th>Strong effect</th>
<th>Metabolic pathway</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CYP3A4/5 inhibition</td>
<td>Imatinib, dasatinib</td>
<td>CML</td>
</tr>
<tr>
<td></td>
<td>P-gp inhibition</td>
<td>Cabozantinib</td>
<td>Kidney cancer</td>
</tr>
<tr>
<td></td>
<td>CYP3A4/5 induction</td>
<td>Enzalutamide</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Moderate effect</td>
<td>CYP3A4/5 inhibition</td>
<td>Pazopanib</td>
<td>Kidney cancer</td>
</tr>
<tr>
<td></td>
<td>P-gp inhibition</td>
<td>Abemaciclib</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>CYP3A4/5, P-gp inhibition</td>
<td>Crizotinib</td>
<td>NSCLC</td>
</tr>
<tr>
<td></td>
<td>CYP3A4/5, P-gp induction</td>
<td>Dabrafenib, Brigatinib</td>
<td>Melanoma and NSCLC</td>
</tr>
</tbody>
</table>

Strong CYP 3A4/5 inhibitors may increase the AUC of substrates five-fold or more. Strong inducers may decrease the AUC of substrates by 80% or more

Anticoagulation management with direct oral anticoagulants in patients with cancer associated venous thromboembolism and renal insufficiency

Renal elimination varies between anti-Xa DOACs: 50% for edoxaban, 36% for rivaroxaban and 27% for apixaban.

Bleeding is more common in patients with higher anti-Xa DOACs peak levels.

In patients with intermediate clearance between 30 and 49 ml/min, anti-Xa DOACs are relatively well tolerated without dose adjustment.

Full doses of anti-Xa DOACs are contraindicated by European recommendations when creatinine clearance is below 30 ml/min for rivaroxaban and edoxaban, or 25 ml/min for apixaban.

On the contrary, the US Food and Drug Administration (FDA) allows apixaban use up to 15 ml/min in VTE.

Studies are still ongoing, and efforts to detect drug–drug interactions must be maintained given the risk of drugs accumulation.

Rivaroxaban and Apixaban anti-Xa chromogenic assay

Table. Plasma Concentrations of Rivaroxaban in Patient Populations Studied(1)

<table>
<thead>
<tr>
<th>Patient population/clinical setting</th>
<th>Rivaroxaban dose</th>
<th>C min (ng/mL)* trough plasma concentration (predose)</th>
<th>C max (ng/mL)** peak plasma concentration (postdose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE prevention after total hip replacement surgery</td>
<td>10 mg once daily</td>
<td>9 (1-38)</td>
<td>125 (91-156)</td>
</tr>
<tr>
<td>DVT treatment (continued treatment)</td>
<td>20 mg once daily</td>
<td>26 (6-87)</td>
<td>270 (189-419)</td>
</tr>
<tr>
<td>Stroke prevention in patients with non-valvular AF (CR-CL &gt; or =50 mL/min)</td>
<td>20 mg once daily</td>
<td>44 (12-137)</td>
<td>249 (194-343)</td>
</tr>
<tr>
<td>Stroke prevention in patients with non-valvular AF (CR-CL 30-49 mL/min)</td>
<td>15 mg once daily</td>
<td>57 (18-136)</td>
<td>229 (178-313)</td>
</tr>
<tr>
<td>Secondary prevention in patients with acute coronary syndrome</td>
<td>2.5 mg twice daily</td>
<td>17 (6-37)</td>
<td>46 (28-70)</td>
</tr>
</tbody>
</table>

Median (6th-95th percentile)

Table. Predicted Apixaban Steady-State Exposure Concentrations(1)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Apixaban C min (ng/mL) trough plasma concentration (predose)</th>
<th>Apixaban C max (ng/mL) peak plasma concentration (2-4 hours postdose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of VTE: elective hip or knee replacement surgery</td>
<td>2.5 mg twice daily</td>
<td>51 (23-109)</td>
</tr>
<tr>
<td>Prevention of stroke and systemic embolism: NVAF</td>
<td>5 mg twice daily</td>
<td>79 (34-162)</td>
</tr>
<tr>
<td>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE)</td>
<td>2.5 mg twice daily</td>
<td>103 (61-230)</td>
</tr>
<tr>
<td>5 mg twice daily</td>
<td>65 (22-177)</td>
<td>132 (69-302)</td>
</tr>
<tr>
<td>10 mg twice daily</td>
<td>120 (41-335)</td>
<td>251 (111-572)</td>
</tr>
</tbody>
</table>

Median (6th-95th percentile)

*** Therapeutic reference ranges have not been established***

These are “on-therapy” levels
Phase 3 clinical trials with factor XI inhibitors in patients with cancer associated venous thromboembolism

The phase 3 trials with FXI inhibitors in VTE are focused on abelacimab, which is being tested against apixaban or dalteparin in patients with cancer-associated VTE.

Abelacimab is a fully humanized monoclonal antibody that binds to FXI with high affinity and locks it in the zymogen confirmation, preventing its activation by FXIIa and thrombin.

It has been evaluated in 3 phase I human studies and 2 phase II studies and is found to be safe and promising.

The pharmacokinetics and pharmacodynamic models obtained from phase I/II studies showed that abelacimab has a half-life of approximately 20 days.

Intravenous administration produces rapid and dose-dependent inhibition of FXI.

No infusions were stopped due to hypersensitivity reactions and no anti-drug antibodies were detected.

Phase 3 clinical trials with factor XI inhibitors in patients with cancer associated venous thromboembolism

The phase 3 trials with FXI inhibitors in VTE are focused on abelacimab, which is being tested against apixaban or dalteparin in patients with cancer-associated VTE.

ASTER (a study comparing abelacimab to apixaban in the treatment of cancer-associated VTE) is a trial that compares abelacimab (150 mg intravenously followed by 150 mg subcutaneously once a month) with apixaban (10 mg BID for 7 days, then 5 mg BID) in 1655 patients with cancer-associated VTE who can take apixaban (https://www.clinicaltrials.gov; NCT05171049)

MAGNOLIA (a study comparing abelacimab to dalteparin in the treatment of gastrointestinal/genitourinary cancer-associated VTE) is a trial that compares abelacimab (at the same dose as in ASTER) with dalteparin (200 units/kg QD for the first month, then 175 units/kg QD) in 1020 patients with gastrointestinal/genitourinary cancer-associated VTE who have a high risk of bleeding (https://www.clinicaltrials.gov; NCT05171075)
Factor XI inhibitors have the potential of being safer than direct oral anticoagulants as the intrinsic pathway is probably dispensable for normal hemostasis but is likely a major contributor of pathological thrombosis.

Questions?

rivera.candido@mayo.edu