Anticoagulation in Cancer Associated Thrombosis

Consensus, Opinions, Current Practices and Future

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Disclosure

- I have no financial relationships to disclose
- I will be discussing off label use of medications
Agenda

• Pertinent Questions to Set the Stage!
• Anticoagulation cascade and mechanism of action of drugs under discussion
• Treatment of cancer associated thrombosis (C.A.T)
  - Scope of the problem
  - Consensus guidelines (NCCN, ACCP, ASCO, ISTH, ESMO)
  - Review data for secondary prevention
  - VTE Treatment in Special Populations
  - Review data with direct oral anticoagulants (DOAC)
  - Ongoing clinical trials with DOAC
• Contraindications to therapeutic anticoagulation treatment
• Answers to the Questions

www.cancercenter.com
Case#1

- 54 YO man with metastatic adenocarcinoma of the lung
- Two cycles of chemotherapy, restaging CT: PE in right lower lobe segmental artery
- Patient is fatigued with a cough, HR 85 bpm, bp128/72, RA O2 sat 96%. BNP normal
- CT demonstrates response, plans are to continue with the current treatment regimen
Incidental PE

Should this patient be treated with anticoagulation?

A. Yes
B. No
C. I don’t know
Preferred Anticoagulation Agent in Cancer Patient

What is the preferred anticoagulation agent in this patient with cancer?

A. Low-molecular weight heparin (LMWH)
B. Unfractionated heparin (UFH)
C. Warfarin
D. Direct oral anticoagulants (DOAC)
E. All of the above
Coagulation Cascade - Basics

Wound

F7a + Tissue factor

Fibrinogen to Fibrin monomers to polymers

F10a → F8a → F9a

F2a → F5a → F11a → F12a
Mechanism of Action of Anticoagulation Agents

Wound

F7a + Tissue factor

LMWH formulations
• Enoxaparin
• Tinzaparin
• Dalteparin
Indirect anti-10a>anti-2a

Fondaparinux - indirect anti-F10a

Direct Oral A C
Rivaroxaban
Apixaban
Edoxaban
Dabigatran

Direct anti-F10a

Direct anti-F2a

Fibrinogen → Fibrin

Direct anti-F10a

F10a → F8a

F9a → F11a

Unfractionated heparin + antithrombin III plus..

Warfarin Anti-F2a,F7a,F9a, F10a

F12a
Scope of the Problem

- Thrombotic events are the second leading cause of death in cancer patients.
- VTE risk is increased 4- to 8-fold in cancer patients compared to the general population.
- Despite appropriate anticoagulation, cancer patients have a 3-fold increased risk of recurrent VTE (up to 21% per year).
- VTE is associated with an up to 6-fold decrease in survival compared to cancer patients without VTE.
Pathogenesis

Virchow’s triad
(modified for cancer patients)

Venous Stasis

Endothelial damage

Hypercoagulopathy

Therapeutic Anticoagulation Treatment for VTE

**Acute Management:** At diagnosis or during diagnostic evaluation:

- **LMWH (preferred)**
  - Dalteparin (200 units/kg SC daily; maximum dose: 18,000 units)
  - Enoxaparin (1 mg/kg SC every 12 hours)

- Fondaparinux (5 mg [<50 kg]; 7.5 mg [50-100 kg]; 10 mg [>100 kg] SC daily)
- Unfractionated heparin IV (80 units/kg load, then 18 units/kg/h, target aPTT of 2-2.5 x control or per hospital standard operating procedures [SOPs])
- Unfractionated heparin SC 333 units/kg load, then 250 units/kg every 12 hours
- **DOAC are not recommended** (apixaban, edoxaban, rivaroxaban and dabigatran require additional clinical experience and research to provide data regarding risks/benefits and guidance for their safe and effective use in cancer patients)
Therapeutic Anticoagulation Treatment for VTE continued

Chronic Management:

- LMWH (category 1) is preferred for the first six months as monotherapy without warfarin in patients with proximal DVT or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer
- Warfarin (2.5-5 mg every day initially, subsequent dosing based on INR value; target INR 2-3)
  - If warfarin is selected for chronic anticoagulation, initiate warfarin concurrently with the parenteral agent used for acute therapy and continue both therapies for at least 5 days and until the INR ≥2 for 24 hours
  - During the transition to warfarin monotherapy, the INR should be measured at least twice weekly. Once the patient is on warfarin alone, the INR should be measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR between 2 and 3, INR testing can be gradually decreased to a frequency no less than once monthly
- DOAC are not recommended (apixaban, edoxaban, rivaroxaban and dabigatran require additional clinical experience and research to provide data regarding risks/benefits and guidance for their safe and effective use in cancer patients)
Therapeutic Anticoagulation Treatment for VTE continued

**Duration of Anticoagulation as Recommended by Guideline:**

- Minimum time of **3 months**
- For **non-catheter-associated** DVT or PE recommend indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist
- For **catheter-associated thrombosis**, anticoagulate as long as catheter is in place. Recommended total duration of therapy is at least 3 months
- Providers should continue to discuss with patients the **risks/benefits of anticoagulation** to determine the appropriate duration of therapy
ACCP Guidelines 2016

- In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over Warfarin therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

Chest. 2016 Feb;149(2):315-52
ACCP Guidelines: Duration of Therapy

• In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).

Chest. 2016 Feb;149(2):315-52
ACCP Guidelines : Bleeding Risk without Stop Date in >3 months therapy

- **Low**
  - no bleeding risk factors; **0.8%** annualized risk of major bleeding

- **Moderate**
  - one bleeding risk factor; **1.6%** annualized risk of major bleeding

- **High**
  - two or more bleeding risk factors; **≥6.5%** annualized risk of major bleeding

*Chest. 2016 Feb;149(2):315-52*
CLOT Trial: Study Design

Control Group

- LMWH
- Vitamin K antagonist (INR 2.0 to 3.0)

CLOT Trial:
- Study Design
- N=672

- Dalteparin 200 IU/kg OD then ~150 IU/kg OD
- 5 – 7 days, 1 month, 3 months, 6 months
CLOT Trial

Risk reduction 52%

672 patients
Solid tumors
Chemo-rx

CLOT Trial: Dalteparin

- Significant reduction in the rate of recurrent VTE at six months
  - 9 vs. 17%
- There were no significant differences in the rates of major bleeding
  - 6 vs. 4%
- There were no significant differences in the overall mortality
  - 39 vs. 41%
CLOT Trial

- **Warfarin group:**
  - Percent time in therapeutic INR range (TTR) **46%**, mean INR 2.5 +/- 0.75
  - Below therapeutic range 30% of time
  - Above therapeutic range 24% of time
  - **20 of 53** recurrent thrombotic events occurred with INR < 2.0
  - Most recurrent events occurred within **first month** of therapy
  - Re-analysis using Fine/Grey instead of KM, **only 30% risk reduction**

CATCH Trial: Study Design

Prospective, randomized open-label, with blinded central adjudication

Inclusion Criteria
- 18 yr or older
- proximal DVT
- PE
- active cancer
- ECOG 0, 1, 2
- informed consent

Clinic visits:  Day 0 7 14 Mo 1 T 2 T 3 T 4 T 5 T 6

- Telephone contacts at 2 weeks after every monthly visit (T)
- Structured interviews to ascertain if outcome events occurred
- INR performed at least once every 2 weeks

Tinzaparin 175 IU/kg once daily

Warfarin (target INR 2 – 3) + Initial tinzaparin 175 IU/kg x 5–10 days

JAMA. 2015 Aug;314(7):677-86
Recurrent VTE

HR 0.65 (95% CI 0.41–1.03)
Wald’s test p = 0.07
Risk reduction = 35%

warfarin, 10.5% (45 events)
TTR 47%
tinzaparin, 7.2% (31 events)
## Safety Outcome Analyses

<table>
<thead>
<tr>
<th>Event</th>
<th>Tinzaparin n/N</th>
<th>Warfarin n/N</th>
<th>HR</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>13/449</td>
<td>12/451</td>
<td>0.89</td>
<td>[0.40, 1.99]</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>50/449</td>
<td>73/451</td>
<td>0.69</td>
<td>[0.49, 0.96]</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>150/449</td>
<td>138/451</td>
<td>1.08</td>
<td>[0.85, 1.36]</td>
</tr>
</tbody>
</table>

HR, hazard ratio: tinzaparin / warfarin. Competing risk regression analyses adjusting for region, tumor stratum, and history of VTE.

JAMA. 2015 Aug;314(7):677-86
CATCH Trial: Conclusion

- Rate of VTE recurrence was lower with tinzaparin (7 vs. 11 percent) at six months, it was not statistically significant.
- Lower rates of clinically relevant non-major bleeding were seen in patients on tinzaparin
- No differences were reported in rates of major bleeding
- No differences were reported in mortality
LMWH vs Warfarin

- Patients in CLOT and CATCH failed warfarin management, but not always warfarin anticoagulation

- Warfarin is an acceptable anticoagulant for selected patients with cancer (cost, convenience, after acute phase in patients without d-d interactions)

JAMA. 2015 Aug;314(7):677-86
Warfarin
INR – Highs and Lows = Bleeds & Recurrent VTE, respectively

- Chemotherapy agents that affect drug metabolism
- Inconsistent dietary intake due to anorexia, nausea or vomiting
- Low body weight
- Low albumin
- Nonadherence with monitoring
Treatment of VTE in Special Populations

- **Elderly (>age 75 years)** - increase bleeding risk
- **Obese**
  - LMWH and fondaparinux should be dosed to actual body weight
  - Dose-capping is not recommended for LMWH
  - **Fondaparinux** should be dose-capped at 10mg daily for patients >100kg
  - Confirm proper dosing with peak factor Xa levels in patients above weight thresholds (>144kg for enoxaparin, >190kg for dalteparin)

## Treatment of VTE in Special Populations

### Renal insufficiency

<table>
<thead>
<tr>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CrCl \geq 30 \text{ mL/min}$ – safe to use without factor Xa monitoring</td>
<td>$CrCl \geq 30 \text{ mL/min}$ – safe to use without factor Xa monitoring</td>
<td>$CrCl \geq 50 \text{ mL/min}$ – safe to use without factor Xa monitoring</td>
</tr>
<tr>
<td>$CrCl 20-29 \text{ mL/min}$ – consider decreasing dose to 1 mg/kg daily and confirm with factor Xa level</td>
<td>$CrCl 20-29 \text{ mL/min}$ – empiric dose reduction not recommended but confirm appropriate dosing with factor Xa level</td>
<td>$CrCl 30-49 \text{ mL/min}$ – empiric dose reduction not recommended but confirm appropriate dosing with factor Xa level</td>
</tr>
<tr>
<td>$CrCl &lt;20 \text{ mL/min}$ – avoid use</td>
<td>$CrCl &lt;20 \text{ mL/min}$ – avoid use</td>
<td>$CrCl &lt;30 \text{ mL/min}$ – avoid use</td>
</tr>
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Thrombocytopenia (platelets <50K)

Acute VTE (diagnosed within 1 month)
- If able to transfuse platelets to >50K, give full-dose anticoagulation
- If unable to transfuse platelets to >50K, consider IVC filter or reduce LMWH to 50% of therapeutic dose

Subacute VTE (diagnosed 1-3 months ago)
- If platelets 25K to 50K, reduce LMWH to 50% of therapeutic dose
- If platelets <25K, consider IVC filter

Chronic VTE (diagnosed >3 months ago)
- If platelets 25K to 50K, reduce LMWH to 50% of therapeutic dose
- If platelets <25K, hold anticoagulation

Treatment of VTE in Special Populations
Intracranial lesion(s)

- Most primary or metastatic brain tumors are not an absolute contraindication to anticoagulation

- Avoid anticoagulation in patients with active or prior intracranial bleeding and high-risk tumor types (e.g. melanoma, RCC, choriocarcinoma, thyroid) especially in untreated or large

- Consider IVC filter in very high-risk patients with LEDVT (Poor CP reserve, high risk tumors)
Treatment of VTE in Special Populations

Catheter-associated thrombosis

CVC still required, properly positioned and functional?  

Yes → Keep CVC in place and initiate anticoagulation (LMWH preferred)

No → Remove the CVC and anticoagulate for 3 months (LMWH preferred)

Improvement of symptoms (e.g. pain, edema) within 1-2 weeks?  

Yes → Anticoagulate for 3 months (consider anticoagulating for as long as CVC remains)

No → Remove the CVC and anticoagulate for 3 months

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# Recurrent VTE while on Anticoagulation—Now what?

<table>
<thead>
<tr>
<th>Clinical context</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of warfarin</td>
<td>Switch to LMWH</td>
</tr>
<tr>
<td>Failure of daily-dosed enoxaparin</td>
<td>Switch to twice daily enoxaparin</td>
</tr>
<tr>
<td>Failure of inappropriately-dosed LMWH</td>
<td>Re-dose LMWH based on weight and renal function</td>
</tr>
<tr>
<td>Failure of appropriately-dosed LMWH</td>
<td>Increase dose by 20-25%</td>
</tr>
</tbody>
</table>

DOAC Use in Cancer Patients?

- No dedicated studies
- Limited data derived from sub-analysis of pivotal VTE studies, 4-6% of total populations
- One phase II “prevention” study: apixaban for VTE prophylaxis in ambulatory cancer patients x 12 weeks
  - Small number of patients, closed due to low accrual
  - Minimal increase in bleeding
  - Not designed for efficacy evaluation

DOAC Use in Cancer Patients?
Systematic Review & Meta-analysis up to 2013

• The primary outcome of the analysis was recurrent VTE
• Data on major bleeding & clinically relevant nonmajor bleeding were analyzed
• Six studies were included in the meta-analysis
• N = 1,132 patients

Chest. 2015 Feb;147(2):475-83.
DOAC vs. Conventional Therapy
Systematic Review & Meta-analysis up to 2013

• Recurrent VTE in Cancer Patients
  • 23 of 595 (3.9%) patients with DOAC
  • 32 of 537 (6.0%) patients with conventional treatment

Chest. 2015 Feb;147(2):475-83.
DOAC: Bleeding in Cancer VTE Systematic Review & Meta-analysis up to 2013

• Major bleeding
  – 3.2% of patients receiving DOACs
  – 4.2% of patients receiving conventional treatment

OR 0.77; 95% CI, 0.41-1.44

Chest. 2015 Feb;147(2):475-83.
Recommendations

- **DOACs:** Use in carefully selected patients
  - Low thrombotic risk tumor type
  - No drug-drug interactions
    - Tamoxifen
    - Dexamethasone
    - Some TKIs
  - No expected fluctuation in renal status
  - Patients understand that there are limited data
Studies in Progress with DOAC

- **DOAC in cancer associated thrombosis**
  - Rivaroxaban in the Treatment of Venous Thromboembolism (VTE) in Cancer Patients (NCT02583191)
  - Apixaban or Dalteparin in Reducing Blood Clots in Patients With Cancer Related Venous Thromboembolism (NCT02585713)
  - PCORI Pragmatic effectiveness study (see next slide)
Eligibility:
1. VTE diagnosis within 30 days
2. An advanced solid tumor malignancy or, a recent (within 6 months) diagnosis of a solid tumor requiring surgery, radiation, chemo or hormone therapy
3. No active/ongoing bleeding or platelet count less than 50,000

Randomized Intervention Arm:
MD/patient choose a DOAC:
  • Rivaroxaban
  • Apixaban
  • Edoxaban

Select Intervention
MD/patient choose a DOAC:
  • Rivaroxaban
  • Apixaban
  • Edoxaban

Randomized Usual Care Arm:
MD patient choose:
  • Continued LMWH
  • Warfarin

Select Usual Care:
MD patient choose:
  • Continued LMWH
  • Warfarin

Outcomes at 3 and 6 months:
• Cumulative incidence of recurrent VTE
• Cumulative incidence of major bleeding
• Anticoagulation burden
• Survival

Schema:
DOAC versus LMWH/warfarin therapy to prevent recurrent VTE in patients with cancer: A pragmatic trial

Decline Randomization:
Contraindications to Therapeutic Anticoagulation Treatment

1. Recent central nervous system (CNS) bleed, intracranial or spinal lesion at high risk for bleeding

2. Active bleeding (major): more than 2 units transfused in 24 hours

Relative

• Chronic, clinically significant measurable bleeding >48 hours
• Thrombocytopenia (platelets <50,000/mcL)
• Severe platelet dysfunction (uremia, medications, dysplastic hematopoiesis)
• Recent major operation at high risk for bleeding
• Underlying hemorrhagic coagulopathy
• High risk for falls (head trauma)
• Neuraxial anesthesia/lumbar puncture
Case#1

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- Two cycles of chemotherapy, restaging CT: **PE in right lower lobe segmental artery**
- Patient is fatigued with a cough, HR 85 bpm, bp128/72, RA O2 sat 96%. BNP normal
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C. Warfarin
D. Direct oral anticoagulants (DOAC)
E. All of the above
Answer Case #1

- 75% of cancer patients found to have unexpected PE in retrospect had symptoms that were attributed to cancer or treatment
- No difference in VTE recurrence rate, bleeding, or mortality in treated patients with symptomatic vs asymptomatic PE
- Incidental PE has similar worse outcomes as symptomatic PE when compared to cancer patients without VTE
- LMWH (category 1 NCCN and Grade 2C AT10) is preferred for the first six months as monotherapy

O’Connell JCO 2006
den Exter JCO 2011
Summary

• **Acute VTE**
  – LMWH to start
  – Continue if on chemotherapy with strong interactions with warfarin: taxol, gemcitabine, adriamycin
  – Warfarin acceptable especially if no alternative
  – **No IVC filters** unless anticoagulation an absolute contraindication and lower Ext VTE. Retrievable preferred over permanent if reasonable prognosis.

• **After 1-3 months**
  – **Continue LMWH**, but no need for prolonged bid injections, even if persistent cancer and active treatment
  – Consider transition to warfarin if comfortable
  – May consider transition to DOAC in carefully selected patients (data from MSKCC)  

Abstract #431 ASH 2015
Summary

- LMWH may have only a slight edge over warfarin in many patients for chronic anticoagulation in controlled setting (but practical aspects?)
- Results of large trials of DOAC vs LMWH in cancer patients needed before we can confidently use in all cancer patients

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Thank you

Cancer Treatment Centers of America

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www.cancercenter.com
Thank you for your attention

First Do No Harm
Syed A. Abutalib, MD

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