Update on treatment of venous thromboembolism in cancer patients

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No conflicts to declare
Outline

- Background
- 3 recent trials on DOAC therapy for treating VTE in cancer patients
- Updated guidelines:
Mr. D is a 68 year old male

- PMH:
  - HTN and CKD stage 3
  - stage I SCLC s/p surgical resection
    - etoposide and cisplatin.
    - Nausea controlled with Zofran

Recent admission for DVT
1st DVT discharged on LMWH
Doc, do I really need to continue these injections?
I find them very uncomfortable,
but I can do it if you really think I should.
And how long do I need to be on the medication?
Background - VTE in Cancer patients

- 20-30% of VTE associated with cancer
- Cancer treatments further increase VTE risk
  - cytotoxic chemotherapy, hormonal therapy, radiation, surgery, use of central venous catheters
  - ↑ 4-7x risk of VTE
  - ↑ 3-4x risk of VTE recurrence

- Cancer patients:
  - VTE second leading cause of death
  - ↑ 2x risk of major hemorrhage on anticoagulation
LMWH for cancer-associated VTE

- LMWH has been standard of care for treatment of cancer-associated VTE for the past 15 years.

- Compared to Coumadin, LMWH has
  - lower rates of VTE recurrence
  - less interactions with chemotherapy agents
  - Does not rely on GI absorption
  - (lower/similar/higher rates of bleeding)

- Numerous real-world hurdles
  - Discomfort and cost
  - Inadequately treated
4 DOACs approved for DVT/PE 2014-2017
- rivaroxaban, apixaban, edoxaban, dabigatran
- Few cancer patients studied

Recent studies on use of Xa inhibitors for VTE in cancer patients are promising.
**Study Definitions**

- **Major Bleed:**
  
  Acute, clinically overt bleeding accompanied by one or more of the following:
  
  - Decrease in Hemoglobin $\geq 2$ g/dL over 24 hours
  - Transfusion of $\geq 2$ Units of pRBC
  - Bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, retroperitoneal)

- **Severe major bleed:**
  
  - Clinical emergency: bleeding with hemodynamic instability or intracranial bleed with neurologic symptoms
  - Or leading to death

- **Clinically Relevant Non-Major Bleeding (CRNMB)**
  
  - Clinically overt episodes (ie GI bleed, hemoptysis, hematuria, epistaxis)
  - Do not meet criteria for major bleed
  - Associated with medical intervention, contact with physician, interruption/discontinuation of drug, or discomfort or impairment of activities
Studies on Xa inhibitors vs LMWH

1. Hokusai VTE: Edoxaban
2. Select- D: Rivaroxaban
3. Carvaggio: Apixaban

"Try to find something that works like aspirin but costs much more."
Direct Factor Xa Inhibitors
Rivaroxaban, Apixaban & Edoxaban

Intrinsic activation
- Surface contact
  - Factor XII
  - Factor XI
  - Factor VIII
  - Factor IXa
  - Factor X

Extrinsic activation
- Vessel injury
  - Factor VII

Prothrombin → Factor Xa → Thrombin → Fibrinogen → Fibrin

Rivaroxaban Apixaban Edoxaban

Low-molecular-weight heparin
Pentasaccharide sequence
Antithrombin
Hokusai- VTE Cancer Trial

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

- Patients: acute symptomatic/incidental VTE in patients with active cancer

1050 Patients underwent randomization

5 days dalteparin

525 Were assigned to the edoxaban group
525 Were assigned to the dalteparin group

6 months
Primary outcomes:

Edoxaban found to be non-inferior in reducing rate of recurrent VTE
- 7.9% (41 patients) of edoxaban patients vs. 11.3% (59 patients) in dalteparin

Safety outcome:
- Rates of major bleed significantly higher in edoxaban group
  - 6.9% (36 patients) of edoxaban patients vs. 4% (21 patients) in dalteparin group
  - Difference mainly due to upper GIB in patients with GI cancer
- Clinically relevant non-major bleed higher in DOAC (14.6 vs. 11.1%)
- Rates of severe major bleeding and survival rates similar in both groups
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)

- Randomized, open-label, multicenter study. Enrolled Sept 2013- Dec 2016

- Patients: active solid or hematologic malignancy with symptomatic lower extremity DVT, or symptomatic/incidental PE (406 patients)

- Treatment: Rivaroxaban vs. LMWH (dalteparin) for 6 months
Primary outcome: Rivaroxaban non-inferior to LMWH for preventing recurrence of VTE

- 6 month recurrence rate was lower 4% in rivaroxaban vs. 11% in dalteparin
Safety outcome:

- Major bleeds numerically higher in DOAC group, mostly GI
  - 11 patients (6%) in rivaroxaban vs.
    6 patients (4%) in dalteparin

- Patients with esophageal or GE cancer more major bleeds with DOAC

Fig 3. Time to major bleed within 6 months.
Clinically relevant non-major bleed 3-fold in DOAC group (4% vs 13%)

<table>
<thead>
<tr>
<th>Criteria to define CRNMB*</th>
<th>Dalteparin (n = 203)</th>
<th>Rivaroxaban (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt bleeding with medical intervention</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Unscheduled contact with a physician</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Interruption or discontinuation of a study drug</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Discomfort or impairment of activities of daily life</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of CRNMB*</th>
<th>Dalteparin (n = 203)</th>
<th>Rivaroxaban (n = 203)</th>
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</thead>
<tbody>
<tr>
<td>GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Upper GI</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lower GI</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Anus</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhoidal</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Genitourinary</td>
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<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Vagina</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Penis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
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<td></td>
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<tr>
<td>Bronchopulmonary</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bruising</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subconjunctival</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Joint effusion</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., Rupert Bauersachs, M.D., Benjamin Brenner, M.D., Adam Torbicki, M.D., Maria R. Sueiro, M.D., Catherine Lambert, M.D., Gualberto Gussoni, M.D., Mauro Campanini, M.D., Andrea Fontanella, M.D., Giorgio Vescovo, M.D., and Melina Verso, M.D., for the Caravaggio Investigators*

ABSTRACT

BACKGROUND
Recent guidelines recommend consideration of the use of oral edoxaban or riva-...
CARVAGGIO trial

- Multinational RCT, investigator-initiated, open-label, noninferiority trial

- Patients
  - Enrolled April 2017-June 2019
  - Newly diagnosed symptomatic or incidental proximal lower limb DVT or PE
  - Patients with active cancer
    - Excluded: basal-cell or squamous cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, acute leukemia

- Trial intervention
  - Apixaban (10 mg bid for 7 days, followed by 5mg bid) vs
  - Dalteparin SQ (200 IU/kg once daily for 1st month, followed by 150 IU/kg daily)
  - Treated for 6 months
Apixaban found to be noninferior to Dalteparin in reducing recurrent VTE

Primary efficacy outcome:

- Recurrent VTE:
  - 5.6% (32 of 576 patients) in apixaban group
  - 7.9% (46 of 579 patients) in dalteparin group

Apixaban more effective than dalteparin for patients < 65 years of age
**Safety outcomes**

- Frequency of major bleeding and major GIB similar in both groups

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dalteparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>3.8% (22 patients)</td>
<td>4% (23 patients)</td>
</tr>
<tr>
<td>Major GIB</td>
<td>1.9% (11 patients)</td>
<td>1.7% (10 patients)</td>
</tr>
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☆ Findings are in contrast to prior DOAC studies ☆
Safety outcomes

Frequency of **clinically relevant non-major bleeding higher in apixaban group**

- 9% (52 patients) in Apixaban group vs.
- 6% (35 patients) in Dalteparin

Mainly GU and upper airways

This finding is consistent with prior DOAC studies

Study was not powered to make definitive conclusion about bleeding
Guidelines for DVT/PE treatment in cancer patients
Considerations: cost, patient preference, bleeding risk, kidney and liver function, type of cancer, type of chemotherapy

- **DOACs** *(preferred for patients without gastric or gastroesophageal lesions)*
  - Contraindications: stage IV/V CKD, active/significant liver disease, platelets <50K, strong dual inhibitors/inducers of CYP3A4 and P-gp
  - Apixaban
    - 10 mg PO bid for 7 days followed by 5 mg PO bid
  - Edoxaban
    - LMWH or UFH for 5 days, followed by 60 mg PO daily
  - Rivaroxaban
    - 15 mg PO bid for 21 days, followed by 20 mg daily

- **LMWH** *(preferred for patients with gastric or gastroesophageal lesions)*
Duration of therapy

- At least 3 months
- Catheter associated: for as long as catheter is in place
- Otherwise, continue as long as active cancer or cancer therapy
- Discuss risks /benefits of prolonged anticoagulation
- LMWH recommended initial treatment for creatinine clearance > 30 ml/min
- For patients without high risk of GI or GU bleeding, rivaroxaban or edoxaban can be used if creatinine > 30 ml/min
Catheter associated: LMWH

Recurrence

- If on LMWH- increase by 20-25% or switch to DOAC
- If on DOAC, switch to LMWH
- If on coumadin, switch to LMWH or DOAC

American Society of Hematology (ASH) guidelines coming soon.
Is Mr. D a good candidate for DOAC therapy:
- No clear contraindications
  - Lung cancer – non GI malignancy
  - CKD III – His GFR is >30
  - Cisplatin/Etoposide chemotherapy - no drug interactions with Xa inhibitors
  - Tolerating chemotherapy - GI absorption not a concern

Duration of therapy: for at least 3-6 months.
- Can discuss risks/benefits of continuing until he is considered in remission
SUMMARY:

- Xa inhibitors have shown to be non-inferior to LMWH in reducing rates of recurrent VTE

- All DOACs showed increase risk of CRNMB compared to LMWH

- Higher risk of major bleeding, GIB with edoxaban and rivaroxaban, particularly with patients with GI cancers
### GI absorption

<table>
<thead>
<tr>
<th>Agent</th>
<th>Absorption site</th>
</tr>
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<tbody>
<tr>
<td>Apixaban</td>
<td>Primary proximal small intestine, Some gastric absorption</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Primary proximal small intestine, Some gastric absorption</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Proximal small intestine</td>
</tr>
</tbody>
</table>

### Exclusion criteria in studies

- Caravaggio trial excluded acute leukemia, brain cancers, brain mets
LMWH still preferred in patients

- where drug-drug interaction is a concern
- GI malignancy
- GI absorption is a concern (frequent vomiting, feeding tubes, gastric/bowel resection)

Coumadin may still be an option for those whose cost is the decision driver, for those with advanced CKD, or for extremes of weight (<50 kg or >150kg)
References:

Thank you
How is My Teaching?

https://tinyurl.com/HowIsMyTeaching