VTE TREATMENT FOR CANCER PATIENTS: TO DOAC OR NOT TO DOAC...THAT IS THE QUESTION

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Central Texas Veterans Healthcare System
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Objectives

• Understand the pathophysiology of hypercoagulable risk in cancer
• Review guideline updates of DOAC use in cancer patients
• Discuss currently recommended treatment options for VTE
• Evaluate clinical data regarding apixaban use in cancer
• Develop recommendations for potential place in therapy of apixaban

Disclosures

• No conflicts of interest to disclose

Definitions Slide

• DOAC- Direct Oral Anticoagulation
• NCCN- National comprehensive Cancer Network
• ASCO- American Society of Clinical Oncology
• LMWH- Low Molecular Weight Heparin
• VTE- Venous thromboembolism
• GIB- Gastrointestinal bleeding

Introduction

• It is known that patients with cancer have an increased risk of VTE
• However, management of VTE is challenging, because the risk of recurrent VTE and bleeding are both increased in this type of patient population
• The reported risk of thrombotic events is 4 times as high in patients with cancer and increases if the patient is receiving chemotherapy, compared with the general population

Pathophysiology of Hypercoagulable Risk in Cancer
Etiology of VTE

Pathophysiology of Hypercoagulable State in Cancer Patients

Estimated Prevalence of VTE in Common Types of Cancer

Practice knowledge

According to the Virchow's Triad diagram, hypercoagulable state is typically seen in which population?

A. Athletes
B. Cancer patients
C. Patients with heart valve disease
D. Patients with history of atrial fibrillation

Clinical Practice Guideline Updates for VTE Treatment in Cancer Patients

2019 ASCO Guideline VTE Treatment

Initial anticoagulation
- Low molecular weight heparin (LMWH) Unfractionated heparin (UFH)
  - Minimum 5 days with edoxaban
  - Minimum 5 days or longer until therapeutic with warfarin
  - Fondaparinux 5-10 days
  - Minimum 5 days or longer until therapeutic with warfarin
  - Rivaroxaban 21 days

Secondary prophylaxis to prevent recurrence for at least 6 months
- LMWH
- Edoxaban or rivaroxaban
- Warfarin
2019 NCCN Guideline VTE Treatment

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Secondary prophylaxis to prevent recurrence for at least 6 months
- LMWH
- Edoxaban or rivaroxaban
- Warfarin
- Apixaban*
- LMWH + Dabigatran*

Guideline recommended DOACs for VTE Treatment in Cancer Patients

Hokusai VTE-Cancer Trial - Edoxaban

Objective
- To compare edoxaban with dalteparin for the treatment of patients with cancer associated VTE

Methodology
- Randomized, open-label, noninferiority
- Compared edoxaban (n=525) with LMWH (n=525) in patients with active cancer who had acute symptomatic VTE for 6 months and followed for 12 months

Primary outcome
- Composite of recurrent venous thromboembolism or major bleeding during the 12 months after randomization, testing the hypothesis that edoxaban would be noninferior to dalteparin for this measure

Inclusion criteria
- Non-basal or squamous-cell skin cancer either active within the prior 6 months or diagnosed within the prior 2 years
- Qualifying VTE
- Intent to administer LMWH for ≥6 months

Exclusion criteria
- Therapeutic anticoagulation for a non-VTE indication prior to randomization
- Active bleeding or contraindication to study drug

Outcomes
- Secondary: Recurrent VTE
  - Edoxaban (7.9%) VS Dalteparin (11.3%)
  - HR 0.71; 95% CI 0.48-1.06; P=0.09
- Primary: Recurrent VTE or Major Bleeding
  - Edoxaban (12.8%) VS Dalteparin (13.5%)
  - HR 0.97; P=0.006 for noninferiority

Hokusai VTE-Cancer Trial – Edoxaban Outcomes
Hokusai VTE-Cancer Trial – Edoxaban
Adverse Events

Major bleeding
Edoxaban (6.9%) VS Dalteparin (4.0%)
HR 1.77; 95% CI 1.03-3.04; P=0.04

Clinically relevant nonmajor bleeding
Edoxaban (14.6%) VS Dalteparin (11.1%)
HR 1.38; 95% CI 0.98-1.94

Major or clinically relevant nonmajor bleeding
Edoxaban (18.6%) VS Dalteparin (13.9%)
HR 1.40; 95% CI 1.03-1.89

SELECT-D Trial - Rivaroxaban
Objective
• To compare rivaroxaban with dalteparin for the treatment of patients with cancer associated VTE

Methodology
• Prospective, randomized, open label, multicenter pilot
• Compared rivaroxaban (n=203) with LMWH (n=203) in patients with active cancer who had symptomatic or incidental VTE for 6 months

Primary outcome
• VTE recurrence at 6 months

SELECT-D Trial - Rivaroxaban
Inclusion criteria
• Active solid tumor or hematologic malignancy
• Cancer defined as cancer other than basal cell or non-squamous cell skin cancer
• Active defined as diagnosis or treatment within prior 6 months, recurrent/metastatic cancer, or cancer not in complete remission

Exclusion criteria
• Current anticoagulation or antiplatelet therapy
• Active bleeding or a high risk of bleeding, contraindicating anticoagulant treatment

SELECT-D Trial - Rivaroxaban
Outcomes
Primary: VTE recurrence at 6 months
Rivaroxaban (4%) VS Dalteparin (11%)
HR 0.43; 95% CI 0.19-0.99

Secondary: Major Bleeding at 6 months
Rivaroxaban (6%) VS Dalteparin (4%)
HR 1.83; 95% CI 0.68-4.96

Edoxaban vs Rivaroxaban

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing for treatment</td>
<td>60 mg once daily after at least 5 days of an injectable anticoagulant or 30 mg once daily</td>
<td>35 mg BID for 21 days, then 20 mg once daily</td>
</tr>
<tr>
<td>Safety considerations</td>
<td>Major bleeds in patients with mucosal tumors or active mucosal lesion Major bleeds in patients with GI and genitourinary malignancies</td>
<td>Major bleeds in patients with mucosal tumors or active mucosal lesions</td>
</tr>
<tr>
<td>Dietary considerations</td>
<td>None</td>
<td>Must take with meal for adequate absorption</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-gp substrate</td>
<td>CYP3A4 &amp; P-gp substrate</td>
</tr>
<tr>
<td>Anticoagulant Reversal</td>
<td>No reversal agent</td>
<td>Andexxa</td>
</tr>
<tr>
<td>Cost</td>
<td>$5</td>
<td>$</td>
</tr>
</tbody>
</table>

Considerations When Choosing a DOAC based on Guideline Recommendation
**Patient Case 1**

A 42 year old female patient with stage IV breast cancer develops a DVT, which of the following options is appropriate:

- a) Plavix
- b) LMWH + Warfarin
- c) LMWH + Edoxaban
- d) Alteplase

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**Dosapixaban have a Place in Therapy for the Treatment of VTE in Cancer Patients?**

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**AMPLIFY Trial – Apixaban**

**Inclusion Criteria**
- Symptomatic VTE,
- Patients with active cancer and history of cancer

**Exclusion Criteria**
- Active bleeding or a high risk of bleeding
- Long-term LMWH treatment deemed to be necessary by the investigator

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**AMPLIFY Trial – Apixaban**

**Objective**
- To perform a subgroup analysis to compare the efficacy and safety of apixaban and enoxaparin followed by warfarin for the treatment of VTE in patients with cancer enrolled in AMPLIFY

**Methodology**
- Randomized, double-blind study compared apixaban (n=88) with enoxaparin + warfarin (n=81) in patients with acute symptomatic VTE for 6 months

**Primary Outcome**
- Recurrent VTE
- VTE-related death and major bleeding

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**AMPLIFY Trial – Apixaban**

**Results**

<table>
<thead>
<tr>
<th></th>
<th>VTE/VTE-related death</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>Apixaban</td>
<td>Enoxaparin/warfarin</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>3.81 (0.75 - 19.78)</td>
<td>0.56 (0.13 - 2.37)</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>0.36 (0.11 - 1.12)</td>
<td>0.45 (0.08 - 2.46)</td>
</tr>
</tbody>
</table>

*This subgroup is based on the patients who have active cancer and/or cancer history (without active cancer)*

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**Patient Case 1**

A 42 year old female patient with stage IV breast cancer develops a DVT, which of the following options is appropriate:

- a) Plavix
- b) LMWH + Warfarin
- c) LMWH + Edoxaban
- d) Alteplase

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**Review of Direct XA Inhibitors**

<table>
<thead>
<tr>
<th>Inhibits Factor Xa</th>
<th>Rivaroxaban ✓</th>
<th>Apixaban</th>
<th>Edoxaban ✓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathway</td>
<td>XII</td>
<td>XII</td>
<td>XII</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Peptidase</td>
<td>Peptidase</td>
<td>Peptidase</td>
</tr>
<tr>
<td>Efficacy</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Safety</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
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AMPLIFY Trial – Apixaban

**Results**

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<th>Major bleeding</th>
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<tr>
<td>Patients, n/ (%)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
</tr>
<tr>
<td>Active cancer</td>
<td>2.87 (2.3)</td>
</tr>
<tr>
<td>Cancer history without active cancer</td>
<td>1.84 (1.5)</td>
</tr>
<tr>
<td>Active cancer and cancer history*</td>
<td>0.30 (0.3)</td>
</tr>
<tr>
<td>No cancer history/no active cancer</td>
<td>2.24 (0.9)</td>
</tr>
</tbody>
</table>

*Aggini G et al. 2015 Intern Soc on Thromb and Haemost 369:799–808

**Strength**

- Well designed randomized, double blind multicenter trial
- Results of this subgroup analysis are consistent with the previous studies

**Limitations**

- Trial excluded patients treated with LMWH only
- Patients enrolled were healthier compared to the other previous
- Only a small number of patients with cancer

ADAM VTE Trial - Apixaban vs Dalteparin

**Objective**

- To investigate the safety of apixaban compared to dalteparin in patients with active cancer

**Methodology**

- A Phase III, Randomized, Open Label Study compared apixaban (n=145) with Dalteparin (n=142) in patients with acute symptomatic VTE for 6 months
- Participants also completed monthly questionnaires to measure satisfaction with the anticoagulation regimen

**Primary and Secondary Outcome**

- Major bleeding
- VTE recurrence

**Inclusion criteria**

- Confirmed acute DVT, PE
- Active cancer defined as metastatic disease and/or any evidence of cancer
- Life expectancy >= 60 days
- Ability to complete questionnaire(s) by themselves or with assistance
- Ability to provide informed written consent
- Willing to return to enrolling institution for follow-up

**Exclusion criteria**

- Treatment with an anticoagulant for more than 7 days for the current blood clot, prior to randomization
- Active bleeding
- Treatment of a thromboembolic event <= 6 months prior to randomization

**McBane et al; Blood 2018 132:421”

**ADAM VTE Trial- Apixaban vs Dalteparin**

*Baseline characteristics*

In the cohort, 65.5% of patients presented with metastatic disease at baseline, and 74% of patients were receiving concurrent systemic cancer therapy. The four most prevalent types of cancer were breast, colorectal, lung, and pancreatic. Only four percent of participants had an upper gastrointestinal malignancy.

*Outcomes*

- **Primary: Major bleeding**
  - Apixaban (0%) VS Dalteparin (2.1%)
  - HR 0.26, 95% CI, 0.09 - 0.80, p = 0.0182

- **Secondary: Recurrent VTE**
  - Apixaban (3.4%) VS Dalteparin (14.1%)
  - HR 0.26, 95% CI, 0.09 - 0.80, p = 0.0182

**Strength**

- Study was specific to cancer
- The use of questionnaires to measure quality of life between apixaban and dalteparin

**Limitation**

- Small number of enrolled patients
- Open-label design
- Reliance on self-reported questionnaire data to evaluate secondary outcomes

**CARAVAGGIO Study- Coming soon**

- An investigator-initiated, multi-national, prospective, randomized, open-label with blind end-point evaluation (PROBE), noninferiority clinical trial
- The primary outcome of the study: recurrent VTE and major bleeding
Recommendations for Potential Place in Therapy of Apixaban

Advantages of Apixaban

- Apixaban vs Rivaroxaban
  - No dietary considerations
  - Dosing
  - Renal function
  - Reduced GIB
- Apixaban vs Edoxaban
  - Reduced GIB
  - Renal function
  - Initial anticoagulation
  - Reversal agent

My Recommendation for DOAC Use

Is patient at increased risk of bleeding?

No
- Rivaroxaban

Yes
- Edoxaban
- Apixaban??

Patient Case 2

A 64 year old male with GI cancer develops a PE, patient has difficulty injecting himself, which of the following options is most appropriate per guideline recommendation;

a) Edoxaban
b) Rivaroxaban
c) Apixaban
d) LMWH

Take Home Points

Rivaroxaban and edoxaban are now recommended options for VTE treatment from both cancer guidelines

Apixaban may be considered as an option based on ongoing trials

Based on data from this presentation when would YOU use apixaban in clinical practice

A. First-line
B. Second-line
C. Last line
D. Never
• **Evaluator:** Chelsey Roscoe, PharmD - PGY2 Ambulatory Care Pharmacy Resident - CommUnityCare

• **Preceptors:** Sarah Rustenhaven, PharmD – Clinical Pharmacy Specialist – Internal Medicine, CTVHCS; Sarah Fry, PharmD – Clinical Pharmacy Specialist - Anticoagulation Clinic, CTVHCS

• **Mentor:** Jennifer Jiang, PharmD – Clinical Pharmacy Specialist – Internal Medicine, CTVHCS