Treatment of DVT* and PE# in cancer: what to do

*DVT, deep vein thrombosis; #PE, pulmonary embolism

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Case presentation

- 69 years old man presents with anorexia, fever, weight loss and night sweats for 1 month
- Medical history: „always healthy“
- Medical/physical examination: 38.1° C, dullness and crackles lung bases, lymphadenopathy of the inguinal region
- Investigations show
  - Hb 9.8 g/dl, PLT 78 G/l, WBC 3.9 G/l
  - eGFR 48 ml/min, gamma-GT und LDH moderately elevated
  - CT imaging shows pleural effusion, mediastinal nodes, retroperitoneal lymphadenopathy and large mass in right fossa illiaca
Case presentation

• Further work-up confirms the diagnosis of a
  • Diffuse large B cell lymphoma (DLBCL), stage IIIB
  • ECOG 2 (largely due to anemia)

• R-CHOP is recommended

• Patient completes 2 cycles of R-CHOP and develops chest pain and shortness of breath
  • PE suspected
Case presentation

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  • PE suspected

• CT pulmonary angiography: Emboli in segmental and subsegmental pulmonary arteries (of the right lung)

What to do? How to treat?
Guidelines
Management and treatment of VTE* in cancer patients

- American College of Chest Physicians (ACCP)
  Kearon C et al., CHEST 2012; 141(2)(suppl):e419S-e494S

- American Society of Clinical Oncology (ASCO)
  Lyman G et al., J Clin Oncoll. 2013; 31:2189-2204

- National Comprehensive Cancer Network (NCCN)

- European Society for Medical Oncology (ESMO)
  Mandala M et al., Ann Oncol. 2011; 22(suppl 6):vi85-92

- International Clinical Practice Guidelines
  Farge D et al., J Thromb Haemost 2013; 11:56-70

*VTE, venous thromboembolism
Overview

- Background

- Standard treatment of venous thromboembolism (VTE) in patients with cancer
  - Challenging issues

- Role of novel/direct oral anticoagulants (NOACs) for treatment of VTE in patients with cancer

- Treatment of catheter-related thrombosis (CRT)
Venous thromboembolism and Cancer

- Cancer is a strong and independent risk factor for venous thromboembolism (VTE)
- Cancer patients account for approximately 20% of all VTE events
- VTE aggravates the clinical course of cancer
  - VTE in cancer patients increases morbidity and mortality
  - One of the leading causes of death in cancer patients
- Management and treatment of VTE in patients with cancer is challenging in clinical practice

Rates of VTE in patients with cancer

- 1 - 20% of patients with cancer develop VTE during the course of their disease

![VTE incidence graph](image)

**VTE-incidence (%)** during a median follow-up of 501 days [IQR, 255-731] in 825 patients with different types of cancer

Ay C et al, J Clin Oncol 2009
When do thrombotic events occur in patients with cancer?

Cumulative probability of VTE

- 3 months: 4.2%
- 6 months: 6.1%
- 12 months: 8.1%
- 2 years: 9.4%

CATS (unpublished)
Risk factors for VTE in patients with cancer

**Cancer-related**
- Cancer site (primary)
- Advanced tumor stage
- High tumor grade
- Initial period after diagnosis

**Treatment-related**
- Major (cancer) surgery
- Hospitalization
- Anticancer treatments (chemotherapy, hormonal therapy, anti-angiogenics)
- Erythropoiesis-stimulating agents
- Central venous catheters
- Transfusions, ...

**Biomarkers**
- Platelet count
- Leukocyte count
- Hemoglobin?
- soluble P-selectin
- D-dimer
- Prothrombinfragment 1+2
- Factor VIII activity
- Thrombin generation potential
- C-reactive protein?
- Microparticles / Tissue factor?
- Mean platelet volume

**Patient-related**
- Age?, gender?, BMI?
- Ethnicity
- Hereditary risk factors (e.g. factor V Leiden mutation)
- Comorbidities
- History of VTE
- Varicose veins

Aims of VTE treatment

• Prevention of acute and chronic complications
  • Fatal PE
  • Thrombus extension and embolisation
    • Improve disease burden (pain, swelling, dyspnea)
• Early and late recurrences of VTE
• Chronic thromboembolic pulmonary hypertension (CTEPH)
• Post-thrombotic syndrome

Anticoagulation is the cornerstone of VTE-treatment
Oral anticoagulation with vitamin K antagonists (warfarin) for treatment of VTE

- High risk of recurrence of VTE and bleeding during oral anticoagulation in patients with cancer

**Recurrence during VKA**
- Hazard ratio (95% CI): 3.2 (1.9-5.4)
- Cancer: 21%
- No Cancer: 7%

**Major bleeding during VKA**
- Hazard ratio (95% CI): 2.2 (1.2-4.1)
- Cancer: 12%
- No Cancer: 5%

Prandoni P, Blood 2002; 100: 3484-8
# Recurrence of VTE and major bleeding in relation to INR

<table>
<thead>
<tr>
<th>INR (range)</th>
<th>Recurrent VTE</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer</td>
<td>No Cancer</td>
</tr>
<tr>
<td>&lt; 2.0</td>
<td>54</td>
<td>15.9</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>18.9</td>
<td>7.2</td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>18.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Overall</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

Number of events per 100 patients/yers

Hutten BA, J Clin Oncol. 2000; 18: 3078-83
Treatment issues of oral anticoagulation (with Vitamin K Antagonists)

• Drug interactions, malnutrition, GI disturbances and liver dysfunctions alter anticoagulant levels in an unpredictable manner (wide fluctuations of INR)

• Thrombocytopenia and invasive procedures require interruption of therapy

• Regular monitoring (INR control)

• Increased risk of recurrence and bleeding
Open-label, randomized controlled trials for treatment of cancer-associated VTE

<table>
<thead>
<tr>
<th>Phase/treatment of VTE</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>LMWH s.c. (3 months)</td>
</tr>
<tr>
<td>Subacute/intermediate</td>
<td>LMWH s.c. (6 months)</td>
</tr>
<tr>
<td>Long-term/chronic</td>
<td>Vitamin K antagonists (Warfarin or Acenocoumarol)</td>
</tr>
</tbody>
</table>

- **CANTHANOX** study: enoxaparin vs. warfarin (3 months)
- **LITE** study: tinzaparin vs. Warfarin (3 months)
- **CLOT** study: dalteparin vs. Warfarin or acenocoumarol (6 months)
- **CATCH** study: tinzaparin vs. Warfarin (6 months)

LMWH, low-molecular-weight heparin

Treatment of cancer-associated VTE
Open-label, randomized controlled trials

- **CANTHANOX**: Enoxaparin 1.5 mg/kg OD
- **LITE**: Tinzaparin 175 U/kg OD
- **CLOT**: Dalteparin 200 IU/kg OD → Dalteparin ~150 IU/kg OD
- **CATCH**: Tinzaparin 175 U/kg OD

1 month → 3 months → 6 months

Meta-Analysis

Risk of VTE recurrence in cancer patients treated with LMWH vs. Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Events, Intervention</th>
<th>Events, VKA</th>
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<tbody>
<tr>
<td>CLOT</td>
<td>0.51 (0.33, 0.79)</td>
<td>27/336</td>
<td>53/336</td>
<td>41.31</td>
</tr>
<tr>
<td>LITE</td>
<td>0.60 (0.23, 1.59)</td>
<td>6/100</td>
<td>10/100</td>
<td>8.37</td>
</tr>
<tr>
<td>Romera</td>
<td>0.61 (0.11, 3.43)</td>
<td>2/36</td>
<td>3/33</td>
<td>2.66</td>
</tr>
<tr>
<td>ONCENOX</td>
<td>0.66 (0.16, 2.74)</td>
<td>4/61</td>
<td>3/30</td>
<td>3.87</td>
</tr>
<tr>
<td>CATCH</td>
<td>0.69 (0.45, 1.07)</td>
<td>31/449</td>
<td>45/451</td>
<td>41.24</td>
</tr>
<tr>
<td>CANTHANOX</td>
<td>0.70 (0.12, 4.09)</td>
<td>2/71</td>
<td>3/75</td>
<td>2.56</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.60 (0.45, 0.79)</td>
<td>72/1053</td>
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Posch and Ay et al. submitted
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<tr>
<td>CANTHANOX</td>
<td>0.44 (0.16, 1.19)</td>
<td>5/71</td>
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<tr>
<td>LITE</td>
<td>1.00 (0.36, 2.75)</td>
<td>7/100</td>
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<td>18.28</td>
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<tr>
<td>CATCH</td>
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<tr>
<td>CLOT</td>
<td>1.57 (0.77, 3.18)</td>
<td>19/338</td>
<td>12/335</td>
<td>30.61</td>
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<tr>
<td>ONCENOX</td>
<td>3.04 (0.38, 24.28)</td>
<td>6/67</td>
<td>1/34</td>
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<tr>
<td>Subtotal (I-squared = 23.1%, p = 0.267)</td>
<td>1.07 (0.66, 1.73)</td>
<td>50/1025</td>
<td>44/995</td>
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Figure 3A: LMWH vs. VKA

Posch and Ay et al. submitted
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<td><strong>100.00</strong></td>
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- LMWH: Low Molecular Weight Heparin
- VKA: Vitamin K Antagonists

Posch and Ay et al. submitted
Guideline recommendations

Treatment and secondary prophylaxis of cancer-associated VTE

• All major consensus guidelines recommend monotherapy with LMWH as the preferred treatment for cancer-associated VTE
  • In the absence of contraindications, LMWH is preferred in the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE
  • For long-term anticoagulation, LMWH for at least 3 to 6 months is preferred because of improved efficacy over VKAs
    • VKAs are an acceptable alternative for long-term therapy if LMWH is not available
  • Anticoagulation beyond the initial 3 to 6 months may be considered for selected patients with active cancer (e.g. metastatic disease, ongoing chemotherapy)

Case presentation

- DLBCL, stage IIIB
- R-CHOP (2 cycles)
- Acute PE

- Anticoagulation with LMWH in therapeutic dosage has been initiated

- Lab investigations 4 days later
  - Hb 8.2 g/dl, PLT 48 G/l, WBC 2.4 G/l, ANC 1.2 G/l
  - eGFR 62 ml/min
Management of cancer-associated VTE in patients with high risk of bleeding

- Cancer- and chemotherapy induced thrombocytopenia

- LMWH is cleared by the kidneys
  → accumulation in patients with impaired renal function (creatinine clearance <30 ml/min).
  - Increased risk for major bleeding in patients with a creatinine clearance of <30 ml/min treated with therapeutic doses of LMWH
  - In patients with severe renal failure (creatinine clearance <25–30 ml) → anti-Xa activity monitoring might be helpful
  - Elevated levels of anti-Xa activity → dose reduction of LMWH
Management algorithm of VTE in patients with cancer and thrombocytopenia

Acute VTE (<1 month) and subacute or chronic VTE (>1 month)

Lee AY. Blood 2013
New options for treatment of DVT/PE

NOAC – New/Novel oral anticoagulants

DOAC – Direct oral anticoagulants

TSOAC – Target-specific oral anticoagulants

NOAC – Non-Vitamin K antagonist oral anticoagulants
NOACs

Mechanism of action

Tissue Factor/Factor VIIa

Factor IX

Factor IXa + VIIIa

Factor X

Factor Xa

+Va

Thrombin (Factor IIa)

Fibrinogen → Fibrin (Thrombus)

Rivaroxaban (Xarelto®)
Apixaban (Eliquis®)
Edoxaban (Lixiana®)

Dabigatran-etiexilate (Pradaxa®)
## NOACs

### New options for treatment of DVT/PE

<table>
<thead>
<tr>
<th>Phase of DVT/PE</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>Vitamin K Antagonant (NMH s.c.)</td>
</tr>
<tr>
<td><strong>Subacute/Intermediate</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic/Long-term</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Conventional“ treatment**

- Dabigatran/Pradaxa® (150 mg BID) (NMH s.c.)
- Rivaroxaban/Xarelto® (15 mg BID for 3 weeks, followed by 20 mg OD)
- Apixaban/Eliquis® (10 mg BID for 1 week, followed by 5 mg BID) (NMH s.c.)

**Switching**

- Edoxaban (60 or 30 mg OD) (NMH s.c.)

**Single-drug approach“**

- Dabigatran/Pradaxa® (150 mg BID) (NMH s.c.)
- Edoxaban (60 or 30 mg OD) (NMH s.c.)
NOACs

Treatment of VTE

• In phase III clinical trials dabigatran, rivaroxaban, apixaban and edoxaban have shown non-inferiority to standard treatment (LMWH/vitamin K antagonist: warfarin) for treatment of DVT and PE
  • Cancer patients comprised only ~4% to 9% of the population in these studies
  • Vitamin K antagonist (warfarin) is a known inferior agent in the treatment of VTE in cancer patients

• No studies available that have specifically addressed the efficacy and safety of NOACs in treatment of cancer-associated VTE
  • Is it premature to use NOACs in cancer patients?

Meta-Analysis

Risk of VTE recurrence in cancer patients treated with NOACs vs. Vitamin K Antagonists

Figure 2B: NOAC vs. VKA

<table>
<thead>
<tr>
<th>Trial</th>
<th>NOAC Odds Ratio (95% CI)</th>
<th>NOAC Events</th>
<th>VKA Events</th>
<th>Meta-Analysis Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOKUSAI</td>
<td>0.52 (0.16, 1.72)</td>
<td>4/109</td>
<td>7/99</td>
<td>0.65 (0.38, 1.09)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>0.58 (0.14, 2.34)</td>
<td>3/81</td>
<td>5/78</td>
<td>0.78 (0.35, 1.76)</td>
</tr>
<tr>
<td>EINSTEIN DVT+PE</td>
<td>0.59 (0.21, 1.68)</td>
<td>6/258</td>
<td>8/204</td>
<td></td>
</tr>
<tr>
<td>RECOVER I+II</td>
<td>0.78 (0.35, 1.76)</td>
<td>10/173</td>
<td>12/162</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (I-squared = 0.0%, p = 0.943) 0.65 (0.38, 1.09) 23/621 32/543 100.00

NOTE: Weights are from random effects analysis
Risk of major bleeding in cancer patients treated with NOACs vs. Vitamin K Antagonists

Figure 3B: NOAC vs. VKA

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>Events NOAC</th>
<th>Events VKA</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>0.46 (0.09, 2.44)</td>
<td>2/87</td>
<td>4/80</td>
<td>13.97</td>
</tr>
<tr>
<td>EINSTEIN DVT+PE</td>
<td>0.49 (0.16, 1.48)</td>
<td>5/257</td>
<td>8/202</td>
<td>32.09</td>
</tr>
<tr>
<td>RECOVER I+II</td>
<td>0.82 (0.28, 2.38)</td>
<td>6/159</td>
<td>7/152</td>
<td>34.20</td>
</tr>
<tr>
<td>HOKUSAI</td>
<td>1.51 (0.37, 6.17)</td>
<td>5/109</td>
<td>3/99</td>
<td>19.74</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.72 (0.39, 1.35)</td>
<td>18/612</td>
<td>22/533</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Hokusai VTE-cancer study

Design features

- Prospective, randomized, open label, blind evaluation study
- LMWH/Edoxaban vs. LMWH (CLOT regimen)
- Primary objective
  - Non-inferiority for combined outcome of recurrent VTE and major bleeding
- Follow-up: 12 months, 1000 pts
- Eligible patients: active cancer or diagnosed within 2 years
Treatment of thrombosis associated with central venous catheters (CVC) in patients with cancer


DOI: 10.1111/jth.12071
Catheter-related thrombosis (CRT)

Treatment

• For the treatment of symptomatic CRT in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting [Best clinical practice].

• The CVC can be kept in place if it is functional, well-positioned and non-infected with good resolution of symptoms under close surveillance; whether the CVC is kept or removed, no standard approach in terms of duration of anticoagulation is established [Best clinical practice].
Conclusions

• Treatment of VTE (DVT and PE) in patients with cancer is challenging

• If vitamin-K-antagonist (VKA) is the treatment of choice, NOACs are acceptable treatment options

• If LMWH is standard, wait for Hokusai VTE-cancer study outcomes before routine use of NOACs
**Summary**

How I treat cancer-associated VTE

**LMWH (therapeutic dose): (3)-6 Monate**

- **Complete Remission**
  - Stop Anticoagulation

- **Active Cancer +/- additional risk factors**
  - Ongoing anti-cancer treatment
  - „Stable disease“ Patient preference
    - Continue LMWH (prophylactic dose)
    - Oral anticoagulants

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Alternative: NOAC

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- **Active Cancer +/- additional risk factors**
  - **Ongoing anti-cancer treatment** → **Continue LMWH (prophylactic dose)**
  - **"Stable disease" Patient preference** → **NOAC or Vitamin K Antagonist**

Alternative: **NOAC**

Thank you for your attention

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