ANTICOAGULATION THERAPY IN CANCER PATIENTS

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Armand Trousseau (1801 – 1867)

- **Trousseau sign of malignancy** is a condition found in certain cancers that is associated with VTE and is characterized by successive tender nodules in affected veins. It is also referred to as **Trousseau syndrome**.
- First described in 1860s.
- Trousseau later developed pancreatic cancer and observed this condition in himself, dying soon thereafter.
Incidence of Cancer in patients presenting with VTE

**PRESENTATION**

- Idiopathic
- Secondary

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Thrombosis in Cancer Patients

- Cancer patients have an approximately 6 fold increase risk of VTE compared to general population.
- The development of a DVT predicts for decreased overall survival in cancer patient population.

Thrombosis in Cancer Patients

- Cancers associated with highest risk of thromboembolism.
  - Malignant brain tumors
  - Adenocarcinomas of lung
  - Ovary
  - Pancreas
  - Colon
  - Stomach
  - Prostate
  - Kidney
  - Hematologic Malignancies
  - Breast on Tamoxifen (2-5x)

Thrombosis in Malignancy

- **CLOT Trial** *(Multicenter randomized, open-label study)*

  - Cancer patients with Proximal DVT/PE
    - Dalteparin @ 1 week then 6mos OAC
    - Dalteparin 1 month then reduced dose for addition 5 months

  Lee, A. NEJM 2003
CLOT trial

- Comparing LMWH versus a coumarin in the prevention of recurrent VTE in cancer patients.
  - 676 cancer patients with new VTE.
  - LMWH bridge 5-7 days then Oral Anticoagulation (OAC) therapy for 6 months.
  - LMWH for 6 months.

- OAC rate of recurrent VTE at 6 months was 17% versus 9% for LMWH.

NEJM 2003 Jul 10; 349(2)
CLOT Trial – Recurrent VTE

6 months

OAC

dalteparin

6 months
CLOT Trial – Bleeding Events

- LMWH – 5.6% Major Bleed (13.6% Any bleed)
- OAC – 3.6% Major Bleed (18.5% Any bleed)

- Neither were statistically significant
Prophylactic OAC in Malignancy

- 5 Randomized Control Trials
  - 1656 patients
  - OAC vs none

- No reduction in mortality at 6 months, 1 year, 2 years, and 5 years.
Prophylactic LMWH in Malignancy

- 9 Randomized Control Trials.
  - 2857 metastatic or locally advanced cancer.
    (1 UFH and 8 LMWH)

No difference in overall survival at 12 months, but Relative Risk was 0.92 (95% CI 0.88-0.97) in favor of LMWH in OS at 24 months.

Development of Symptomatic VTE had RR of 0.55 (95% CI 0.37-0.82) in favor of LMWH.

Major and minor bleeding was not statistically significant between treatment and control groups.
Central Venous Catheters and Malignancies

INCREASED RISK OF THROMBOSIS

- Peripherally inserted > IJ or Subclavian
- Catheter tip too shallow.
- Left sided catheter.
- Prior Radiation Therapy to the Chest.
- Previous CVC.
Central Venous Catheters and Malignancies

• 12 Randomized Control Trials
  • 3611 cancer patients with CVC.
  • Treatment (LMWH, LDUH, LD-VKA) vs none.

Could not confirm or exclude benefit or detrimental effects to prophylactic therapy in cancer patients with CVCs.
Questions

- When to prophylactically anti-coagulate a cancer patients?
- Should cancer patients with CVCs be prophylactically anti-coagulated?
- How to treat a cancer patient with an acute VTE?
- How to treat a cancer patient with an acute catheter associated VTE?
- What about prophylaxis in the travelling cancer patient?
American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition)

GRADE SYSTEM

- Grade 1 = Strong recommendation
- Grade 2 = Less certainty, weaker recommendation.

- A = High-quality evidence
- B = Moderate-quality evidence
- C = low-quality evidence
4.2.1 In outpatients with cancer and without additional risk factors* recommend against prophylaxis with LMWH or LDUH [2B] and against VTA [1B].

4.2.2 Outpatients with solid tumors and risk factors* then recommend LMWH or LDUH prophylaxis [2B].

- Prior VTE, immobilization, Hormonal therapy, Angiogenesis inhibitors, thalidomide or lenolidomide use.
Cancer Patients with CVCs

- Outpatients with cancer and indwelling CVCs, recommendation against prophylaxis with LMWH or LDUH [2B] or VKA [2C].
For prolonged travel in patients with active malignancy...

6.1.1 Frequent ambulation, calf muscle exercises, sitting in aisle seat [2C].

6.1.2 Use of below the knee graduated Compression stockings [2C].

6.1.3 Against use of ASA or anticoagulants [2C].
Acute LE-DVT in Cancer Patient

- **3.1.5** If no high risk for bleeding, then anticoagulation to extend beyond 3 months [1B]. Reassess annually

- **3.2.2** Recommend LMWH over VKA [2B]. VKA over Dabigatran / Rivaroxaban [2B].

- **4.1** Recommend Compression stockings for 2 years [2B].
Administration of LMWH

- 2.5.2. In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C).

- Remarks: This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twicedaily injection). It also places value on avoiding an extra injection per day.
NCCN Guidelines Version 2.2013
Deep or Superficial Vein Thrombosis

DVT/SVT: DIAGNOSIS

DIAGNOSIS
- Clinical suspicion of DVT or SVT:
- Swelling of unilateral extremity
- Heaviness in extremity
- Pain in extremity
- Unexplained persistent calf cramping
- Swelling in face, neck or supraclavicular space
- Incidental DVT/SVT
- Catheter dysfunction (If catheter is present See Catheter-Related DVT (DVT-3))

WORKUP/IMAGING
- Comprehensive medical history and physical examination
- CBC with platelet count
- PT, aPTT
- Liver and kidney function tests
- Venous ultrasound

IMAGING FINDINGS
- Peripheral catheter related
- Non-catheter related

ADDITIONAL IMAGING
- Symptomatic treatment, including warm compresses, anti-inflammatory medications and elevation
- Re-evaluate if there are progressive symptoms
- Close proximity to deep venous system
- Venous imaging:
  - Repeat venous ultrasound
  - CT scan
  - Magnetic resonance venogram (MRV)
  - Venogram

Positive or Indeterminate
- Positive for DVT
  - See Treatment (DVT-2)
- Negative or Indeterminate
  - Venous imaging:
    - Repeat venous ultrasound
    - CT scan
    - Magnetic resonance venogram (MRV)
    - Venogram
  - Positive for DVT
  - Reassurance Evaluate for other causes
  - No
  - Continued clinical suspicion of DVT

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2013
Deep or Superficial Vein Thrombosis

DVT LOCATION

Pelvic/iliac/IVC → Contraindication to anticoagulation
   Yes → IVC filter (retrievable preferred)
   No → Anticoagulation therapy
   Yes → Re-evaluate as clinically indicated

Femoral/popliteal → Contraindication to anticoagulation
   Yes → Graduated compression stockings (GCS)
   No → Anticoagulation therapy

Calf → Contraindication to anticoagulation
   Yes → Follow-up for DVT progression initially at one week
   No → Progression → See Pelvic/iliac/IVC and Femoral/popliteal pathway above
   No progression → Continue to follow as clinically indicated

Upper extremity → Contraindication to anticoagulation
   Yes → Follow until contraindication is resolved or progression of DVT
   No → Anticoagulation therapy
   Yes → Re-evaluate for risk/benefit of anticoagulation

Superior vena cava (SVC) → Contraindication to anticoagulation

Notes:

- See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (VTE-D).
- See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).
- See Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.
- Consider permanent filters only for rare patients with permanent contraindications to anticoagulation or with chronic comorbidities.
- See Elements for Consideration in Decision Not To Treat (VTE-F).

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Acute Pulmonary Embolism in Cancer Patient

- 6.4 If no high risk for bleeding, then anticoagulation to extend beyond 3 months [1B]. Reassess annually.

  If high risk for bleeding, then anticoagulation to extend beyond 3 months [2B]. Reassess annually.
UE Catheter Associated DVT

- 9.3.3 UE DVT with properly functioning CVC that has an ongoing need for use, then recommend not to remove catheter [2C].
- 9.3.2 Recommend anticoagulation therapy for at least 3 months [2B].
- 9.3.3 In patients who have UEDVT that is associated with a central venous catheter that is removed, we recommend 3 months of anticoagulation over a longer duration of therapy in patients with no cancer (Grade 1B), and we suggest this in patients with cancer (Grade 2C).
- 9.3.4 UEDVT that is associated with a central venous catheter that is not removed, we recommend that anticoagulation is continued as long as the central venous catheter remains over stopping after 3 months of treatment in patients with cancer (Grade 1C).
CATHETER-RELATED DVT: DIAGNOSIS AND TREATMENT

**DIAGNOSIS**

- Clinical suspicion of catheter-related DVT
  - Unilateral arm/leg swelling
  - Pain in supraclavicular space or neck
  - Dysfunctional catheter

- No DVT

**WORKUP/IMAGING**

- Ultrasound
- CT/MRI
- Venogram

**TREATMENT**

- Anticoagulate\(^c,e\) for as long as catheter is in place
  - Recommended total duration of therapy is at least 3 mo
  - Consider catheter removal if symptoms persist
  - Consider catheter-directed pharmacomechanical thrombolyis in appropriate candidates\(^e,i\)

- Contraindication to anticoagulation\(^d\)

- No contraindication to anticoagulation\(^d\)

- DVT

- Contraindication to anticoagulation\(^d\)

- Follow for change in contraindication as clinically indicated

- Contraindication resolved

- Re-evaluate for risk/benefit of anticoagulation\(^h\)

- Contraindication persists

- Remove catheter

- Evaluate for other causes
  - Consider further imaging/testing with another modality if clinical suspicion is high and initial imaging failed to show DVT.

\(^c\)See Therapeutic Anticoagulation Treatment for Venous Thromboembolism (VTE-D).

\(^d\)See Contraindications to Prophylactic or Therapeutic Anticoagulation Treatment (VTE-B).

\(^e\)See Anticoagulation Failure (VTE-H), if extension of VTE or new VTE while on recommended anticoagulation therapy.

\(^f\)Choice of regimen should be made based upon institutional expertise/preferences in conjunction with interventional radiology or vascular surgery colleagues (See Thrombolytic Agents [VTE-I]).

\(^h\)See Elements for Consideration in Decision Not To Treat (VTE-F).

\(^i\)See Contraindications to Thrombolyis (VTE-J).

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THE END