Is There a Role for Prophylaxis in Cancer Patients During Therapy?
Disclosures

- Research grants – Bayer, sanofi aventis, sanofi-aventis
- Consulting – Bayer, sanofi-aventis, Biolex, Genentech, Merck, Daiichi, Boehringer-Ingelheim, Covidien, Johnson & Johnson.
1865: Described “phlegmasia alba dolens” as a presenting symptom of occult cancer.

1867: Trousseau developed phlegmasia alba dolens of his left leg and correctly predicted the diagnosis of his own gastric cancer, which subsequently killed him.

Professor Armand Trousseau (1801-1867)
American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer

Gary H. Lyman, Alok A. Khorana, Anna Falanga, Daniel Clarke-Pearson, Christopher Flowers, Mohammad Jahanzeb, Ajay Kakkar, Nicole M. Kuderer, Mark N. Levine, Howard Liebman, David Mendelson, Gary Raskob, Mark R. Somerfield, Paul Thodiyil, David Trent, and Charles W. Francis
Questions Raised by ASCO

(1) Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

(2) Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

(3) Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

(4) What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

(5) Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?
Questions Raised by ASCO

(1) Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?

(2) Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

(3) Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis?

(4) What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

(5) Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Hospitalizations or Patients</th>
<th>VTE Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levitan, et al. 1999*</td>
<td>1,211,944</td>
<td>7,238</td>
</tr>
<tr>
<td>Sallah, et al. 2002</td>
<td>1,041</td>
<td>81</td>
</tr>
<tr>
<td>Stein, et al. 2006</td>
<td>40,787,000</td>
<td>837,000</td>
</tr>
<tr>
<td>Khorana, et al. 2006†</td>
<td>66,106</td>
<td>5,272</td>
</tr>
<tr>
<td>Khorana, et al. 2007</td>
<td>1,015,598</td>
<td>41,666</td>
</tr>
</tbody>
</table>

*Medicare claims data base only includes patients age 65 years.
†Included only patients with cancer with neutropenia.

Patients with cancer have a six-fold increased risk of VTE compared to those without cancer.\textsuperscript{1}

Active cancer accounts for almost 20\% of all new VTE events occurring in the community.\textsuperscript{2}

The risk is especially high in patients with malignant brain tumors and adenocarcinoma of the ovary, pancreas, colon, stomach, lung, prostate, and kidney.

Cancer patients undergoing surgery have at least twice the risk of postoperative DVT and > 3x the risk of fatal PE than noncancer patients undergoing similar procedures.\textsuperscript{1,2}

Cancer is also an independent predictor of failure of postoperative prophylaxis.\textsuperscript{2,3}

Compared to those without cancer, patients receiving cytotoxic or immunosuppressive therapy have a 6.5-fold increased risk of VTE.\(^1\)

Cancer patients receiving chemotherapy account for 13% of the overall burden of VTE in the population.\(^2\)

Khorana AA, Francis CW, Culakova E:
VTE is a leading cause of death in cancer patients receiving outpatient chemotherapy

CONSEQUENCES OF CANCER-ASSOCIATED VTE

- In a prospective observational study of ambulatory cancer patients initiating chemotherapy, venous + arterial thromboembolism accounted for 9% of deaths (1).

- Cancer diagnosed at same time as, or within 1 year of an episode of VTE, is associated with 3-fold increase in mortality at 1 year (2).

- Hospitalized cancer patients with VTE have a greater mortality rate (OR 2.01; 95% CI 1.83 to 2.22; P < 0.0001). This is true with and without metastatic disease (3).

CONSEQUENCES OF CANCER-ASSOCIATED VTE

- VTE in patients with cancer consumes health care resources.

- In a retrospective analysis, the mean length of DVT-attributable hospitalization was 11 days, and average cost of hospitalization for the index DVT episode was $20,065 in 2002 US dollars.

- Reducing VTE in patients with cancer could have a significant impact on morbidity, outcomes, use of health care resources and mortality.

Are there disadvantages of anticoagulation in active cancer patients?

“Patients with cancer require long-term anticoagulation with a two-fold greater risk of bleeding complications than in patients who don’t have cancer.”

Recurrent VTE and Bleeding Complications During Anticoagulant Treatment in Patients with Cancer and Venous Thrombosis.

Patient-related Risk Factors in Cancer Patients

- Older age
- Race (higher in African Americans; lower in Asian-Pacific Islanders)
- Comorbid conditions (obesity, infection, renal disease, lung disease, arterial thromboembolism)
- Prior history of VTE
- Elevated prechemotherapy platelet count
- Heritable prothrombotic mutations

Cancer-related risk factors for VTE

- Primary site of cancer (GI, brain, lung, gynecologic, renal, hematologic)
- Initial 3-6 months after diagnosis
- Current metastatic disease

Treatment-related risk factors for VTE

- Recent major surgery
- Current hospitalization
- Active chemotherapy
- Active hormonal therapy
- Current or recent antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab)
- Current erythropoiesis-stimulating agents
- Presence of central venous catheters

*Bevacizumab is clearly associated with an increased risk of arterial thrombotic events; an association with venous thrombosis is not fully established. However, note recent meta-analysis (Nalluri, et al, JAMA 2008).
7.0 Prophylaxis in Cancer Patients

7.0.1. For cancer patients undergoing surgical procedures, we recommend routine prophylaxis appropriate for the type of surgery (Grade 1A). Refer to

*Advantages favoring LMWHs over UFH in cancer surgery prophylaxis include qd vs. q8h injections and a lower risk of HIT.

7.0.2. For cancer patients bedridden with an acute medical illness, we recommend routine prophylaxis as for other high-risk medical patients (Grade 1A).

ASCO: 1. SHOULD HOSPITALIZED PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS?

Recommendation. Hospitalized patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications to anticoagulation.
2.1 Prophylaxis in Cancer Surgery

2.1.6. For selected high-risk general surgery patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing prophylaxis after hospital discharge with LMWH for up to 28 days be considered (Grade 2A).

Geerts, et al. ACCP Clinical Practice Guidelines Chest 2008
SHOULD AMBULATORY PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS DURING SYSTEMIC CHEMOTHERAPY?

(1) Routine prophylaxis with an antithrombotic agent is not recommended.

(2) Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk for VTE. Until such time as data are available from RCTs, LMWH or adjusted-dose warfarin (INR 1.5) is recommended in myeloma patients receiving thalidomide plus chemotherapy or dexamethasone.

SHOULD AMBULATORY PATIENTS WITH CANCER RECEIVE ANTICOAGULATION FOR VTE PROPHYLAXIS DURING SYSTEMIC CHEMOTHERAPY?

(3) RCTs evaluating antithrombotic agents are needed in patients with multiple myeloma receiving thalidomide or lenalidomide plus chemotherapy and/or dexamethasone.

(4) Research identifying better markers of ambulatory patients with cancer most likely to develop VTE is urgently needed.

60 year-old patient with metastatic breast cancer develops flank pain and leg swelling.
Colon ca resected three weeks prior...
Conclusions

1. Medical and surgical cancer patients are at increased risk for VTE.

2. Prophylaxis is effective and is underutilized. All patients should be screened at admission.

3. Hospitalized, medically ill cancer patients should receive prophylaxis.

4. Cancer surgery patients should be considered for extended prophylaxis after discharge.

5. Cancer patients with proven VTE should be considered for prolonged treatment with LMWH rather than warfarin.

6. *It is unclear if cancer patients receiving outpatient therapy benefit from prophylaxis. It would appear that certain patients may. Until additional data are available, such patients should be individualized.*
“There can only be a limited advantage to encouraging increased alertness for a disease that is usually asymptomatic. Our energies would be more profitably channeled into improving the current dismal rates of prophylaxis……. ”
“...The real problem is not the 10% of patients who survive long enough to receive treatment but the 90% who die in the first hour after the event. For both groups, more systematic prophylaxis is clearly the way forward; treatment is merely the ambulance at the bottom of the cliff.”

-Paul Egermayer
THANK YOU!!!!
2.1.3. For patients with DVT and cancer, we recommend **LMWH** for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A).

For these patients, we recommend subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (also, see Section 2.4) (Grade 1C).