Common Bleeding Disorders in Cancer Patients

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## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/ Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
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<td>Diichi-Sankyo</td>
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<td>Medical Education Speakers Network</td>
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- No, nothing to disclose
- Yes, please specify:
• The Scope of the problem of cancer and bleeding

• Common Causes of Bleeding in Cancer

• Management of Bleeding in Cancer Patients
Cancer and Bleeding: The Scope of the Problem
Cancer Associated Bleeding

• **Gastrointestinal Bleeding**
  > 300,000 hospitalizations (1 - 2% of all US hospitalizations)
  Upper : 50-100/100,000 persons per year
  Lower : 30 – 36/100,000 persons per year
  **10% cancer** (cancer per se or therapy-related)

• **Hemoptysis**
  100/100,000 persons per year
  Cancer discovered in **8% in men and 4.3% in women**

• **Hematuria**
  Cancer discovered in **8% in men and 3.7% in women**

• **Postmenopausal Bleeding**
  5% of all gynecological consultations
  **7 -10% found to have cancer**

Anticoagulant – associated Bleeding

- **Atrial Fibrillation**
  Prevalence: 2.7 – 6.1 millions

- **Coronary Heart Disease**
  Prevalance: 15 millions (≥ 20 years old)

- **Venous Thromboembolism**
  Annual incidence: 104 – 183 /100,000 person-years
  20% of all VTE due to cancer

- **CKD stage 3 (eGFR 30 – 59)**
  Prevalence 6% of general population

- **Bleeding rates (6-12 months):**
  Major: 2.4 – 10.2%
  Clinically Relevant Nonmajor Bleeding: 15 – 20%

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Major Bleeding vs Clinically Relevant Nonmajor Bleeding

**Major Bleeding**
- Fatal bleeding
- Bleeding in a critical area or organ; intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome
- Fall in Hb ≥ 2g/dL or leading to transfusion of ≥ 2 units whole blood or packed RBCs

**Clinically Relevant Nonmajor Bleeding**
- Any signs or symptoms of hemorrhage that does not fit the criteria for major bleeding
- a face-to-face evaluation
- and/or hospitalization or increased level of care
- And/or requires medical intervention

## Major Bleeding & CRNMB rates in Cancer VTE Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Major Bleeding (%)</th>
<th>CRNMB (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>CLOT NEJM 2003 6 months</strong></td>
<td>Dalteparin</td>
<td>VKA</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td><strong>CATCH JAMA 2015 6 months</strong></td>
<td>Tinzaparin</td>
<td>VKA</td>
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<tr>
<td></td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>10.9</td>
<td>15.3</td>
</tr>
<tr>
<td><strong>DALTECAN J Thromb Haemost 2015 (12 months)</strong></td>
<td>Dalteparin</td>
<td></td>
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<tr>
<td></td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td><strong>Houkusai Cancer VTE NEJM 2018 (12 months)</strong></td>
<td>Dalteparin</td>
<td>Edoxaban</td>
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<tr>
<td></td>
<td>4</td>
<td>6.9</td>
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<td></td>
<td>11.1</td>
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<td>14.6</td>
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<tr>
<td><strong>SELECT-D J Clin Oncol 2018 (6 months)</strong></td>
<td>Dalteparin</td>
<td>Rivaroxaban</td>
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</table>
Common Causes of Bleeding in Cancer Patients

University of Texas M.D. Anderson Cancer Center Experience
Vascular Bleeding (Tumor erosion & others)

- Hematochezia, Melena
- Hematemesis
- Epistaxis
- Hemoptysis
- Intracranial hemorrhage
- Hematuria/GU bleeding
Bleeding Consults at M.D. Anderson Cancer Center

- Major Bleeding
- CRNM bleeding
Management of Bleeding in Cancer Patients
Management

- Assessment & treatment sometimes occur simultaneously

- Arrest bleeding

- Venous Access

- Stop all anticoagulants and antiplatelet drugs

- Volume replacement

- **Stat Labs**: CBC, review smear, PT, PTT, fibrinogen, D-dimers, chemistry, type & crossmatch, urgent coag studies (if needed)

- Interventions
Vascular Bleeding (Tumor erosion & others)

- Hematochezia, Melena
- Hematemesis
- Epistaxis
- Hemoptysis
- Intracranial hemorrhage
- Hematuria/GU bleeding

General Measures
- Nonadherent dressings
- Hemostatic dressings
- Hemostastic agents
- Radiotherapy
- Surgery
- Endoscopy
- Interventional radiology
- Adjunctive therapy

Adapted from Pereira J et al. The Oncologist, 2004:9:561-570
Medical Bleeding

- **Platelet Defect**
  - Quantitative (Thrombocytopenia)
  - Qualitative (NSAIDs, M protein)

- **Coagulation Factor Defect**
  - Deficiency
  - Inhibitors (esp. anticoagulants)

- **Fibrinolysis Defect**
  - Hyperfibrinolysis
I. Anticoagulant-associated Bleeding
MD Anderson Experience: Anticoagulant – Associated Bleeding
Anticoagulation Indications

- Valve
- Atrial Fibrillation
- VTE
Onset of Bleeding Complications in VTE patients
Management of Anticoagulant-Associated Bleeding

- General & local measures and stop anticoagulants

Unfractionated Heparin (UFH)
- UFH ½ life = 60-90 minutes
- 1mg of protamine neutralizes 100 IU of UFH

<table>
<thead>
<tr>
<th>Time elapsed since heparin dose</th>
<th>Dose of protamine (mg) to neutralize 100 IU of UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>1.0 – 1.5 mg/100 IU of UFH</td>
</tr>
<tr>
<td>30 – 60 min</td>
<td>0.5 – 0.75 mg/100 IU of UFH</td>
</tr>
<tr>
<td>&gt; 2 hrs</td>
<td>0.25 – 0.375 mg/100 IU of UFH</td>
</tr>
</tbody>
</table>

- Not ≥ 50 mg of protamine
- Monitor APTT
- Second dose may be necessary

## Management of Anticoagulant-Associated Bleeding

**Low-molecular weight heparins (LMWH)**

- LMWH ½ life = 4-7 hours
- Protamine neutralizes 60% of anti-Xa activity

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Time elapsed since LMWH dose</th>
<th>Protamine dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>&lt; 8 hrs</td>
<td>1mg/ 1mg enoxaparin</td>
</tr>
<tr>
<td></td>
<td>8 – 12 hrs</td>
<td>0.5 mg/1 mg enoxaparin</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>&lt; 8 hrs</td>
<td>1mg/ 100 anti-Xa units</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>8 -12 hrs</td>
<td>0.5 mg/100 anti-Xa units</td>
</tr>
</tbody>
</table>

- Not ≥ 50 mg of protamine per dose
- Second dose may be necessary

Management of Anticoagulant-Associated Bleeding

Vitamin K Antagonists (VKA)

- Warfarin ½ life: 20-60 hours

- IV Vitamin K 5-10 mg

- 4F- Prothrombin Complex Concentrate (PCC)
  - INR 2 - 4: 25 IU/kg
  - INR 4 - 6: 35 IU/kg
  - INR > 6: 50 U/kg

- If 4F-PCC not available, fresh frozen plasma 10-15 ml/kg

Adapted from Tomaselli et al. J Am Coll Cardiol 2017;70:3042-3067
Figure 1. Management of direct oral anticoagulant-associated bleeding.

II. Thrombocytopenia
Mechanisms of Thrombocytopenia

- **Decreased bone marrow production of platelets**
  - marrow failure: aplastic anemia, myelodysplasia
  - marrow infiltration: leukemias, myeloma, myelofibrosis
  - myelosuppression: cytotoxic drugs and radiotherapy

- **Increased peripheral destruction of platelets**
  - immune thrombocytopenic purpura (ITP)

- **Consumption thrombocytopenia**
  - heparin-induced thrombocytopenia, DIC, TTP/HUS, HELLP

- **Platelet sequestration**
  - hypersplenism
Relation between Hemorrhage and Platelet Count (92 patients with acute leukemia)

<table>
<thead>
<tr>
<th>Category</th>
<th>PLT count/cmm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 1,000</td>
</tr>
<tr>
<td>B</td>
<td>1,000 – 3,000</td>
</tr>
<tr>
<td>C</td>
<td>3,000 – 5,000</td>
</tr>
<tr>
<td>D</td>
<td>5,000 – 10,000</td>
</tr>
<tr>
<td>E</td>
<td>10,000 – 20,000</td>
</tr>
<tr>
<td>F</td>
<td>20,000 – 50,000</td>
</tr>
<tr>
<td>G</td>
<td>50,000 – 100,000</td>
</tr>
<tr>
<td>H</td>
<td>&gt; 100,000</td>
</tr>
</tbody>
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Curve I: All hemorrhage
Curve 2: Skin hemorrhage & epistaxis excluded
Curve 3: Grossly visible hemorrhage
## Platelet Transfusion Guidelines (ASCO)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Platelet K/cmm</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancies</td>
<td>&lt; 10</td>
<td>Transfuse at higher count – bleeding, fevers, hyperleukocytosis, clotting abnormalities, invasive procedures</td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>&lt; 10</td>
<td>Transfuse at higher levels based on judgement</td>
</tr>
<tr>
<td>Chronic, stable, severe thrombocytopenia (not on therapy, e.g. MDS, Aplastic anemia)</td>
<td></td>
<td>Consider observation; reserve transfusion for episodes of bleeding or during therapy</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>&lt; 10</td>
<td>Transfuse at higher levels if bleeding</td>
</tr>
</tbody>
</table>
| Invasive procedures                             |                | 40-50K for major procedures  
|                                                |                | ≥ 20K for bone marrow biopsy, central line, etc                           |
III. Disseminated Intravascular Coagulation
Disseminated Intravascular Coagulation

- Pathophysiology
  1. extensive endothelial injury
  2. release of thromboplastin-like substances and activation of coagulation cascade
  3. activation of fibrinolysis

- Causes:
  - tissue damage (e.g. trauma)
  - complications of pregnancy (release of tissue factor)
  - neoplasia (tissue factor, protease, TNF, etc)
  - infection
  - vascular disorders
  - immunological (complement activation, tissue factor)
Pathophysiology of DIC

Clotting system activation

XIIa → thrombin → Fibrinogen → Fibrinopeptide A&B + Fibrin monomer → Fibrin multimer

Consumption

thrombocytopenia

Platelet dysfunction

Consumption of Clotting factors

BLEEDING

Kinin generation
# Cancer-associated DIC

<table>
<thead>
<tr>
<th>Predominant type of cancer</th>
<th>Procoagulant</th>
<th>Hyperfibrinolytic</th>
<th>Subclinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic cancer, adenocarcinoma</td>
<td>Acute promyelocytic leukemia (APL), metastatic prostate Ca</td>
<td>Many solid cancers</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Predominant clinical symptom</th>
<th>Procoagulant</th>
<th>Hyperfibrinolytic</th>
<th>Subclinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>DVT, PE, Marantic endocarditis</td>
<td>Bruising, mucosal and internal bleeding, trauma sites bleeding. Hemorrhage – most common cause of induction mortality in APL</td>
<td>Only laboratory abnormalities (↓ PLT, ↓ fibrinogen, ↑ PT/APTT, microangiopathic hemolytic anemia) May remain long-standing; worsen or improve depending on cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Different clinical presentations</th>
<th>Procoagulant</th>
<th>Hyperfibrinolytic</th>
<th>Subclinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features of arterial ischemia, DVT, PE</td>
<td>Bruising, mucosal and internal bleeding, trauma sites bleeding. Hemorrhage – most common cause of induction mortality in APL</td>
<td>Only laboratory abnormalities (↓ PLT, ↓ fibrinogen, ↑ PT/APTT, microangiopathic hemolytic anemia) May remain long-standing; worsen or improve depending on cancer</td>
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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Procoagulant</th>
<th>Hyperfibrinolytic</th>
<th>Subclinical</th>
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</thead>
<tbody>
<tr>
<td>Treat underlying cancer</td>
<td>Treat underlying cancer</td>
<td>Treat underlying cancer</td>
<td>Treat underlying cancer</td>
</tr>
<tr>
<td>Anticoagulation with heparin</td>
<td>Supportive care with blood products</td>
<td>? Anticoagulation with heparin</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Thachil et al. J Thromb Haemost 2015;13:671-675
Management of Acute (Hyperfibrinolytic) DIC

- Supportive therapy as required (e.g. volume replacement)

- Replacement therapy
  - platelet transfusion
    - < 50 (if bleeding) or
    - < 30 in APL or < 20 in other cancers (at high risk of bleeding)
  - cryoprecipitate/fibrinogen concentrate to replace fibrinogen
  - FFP to replace other factors

- Monitor response with CBC, PTT, PT, fibrinogen

- Specific therapy: eg. *All trans-retinoic acid in APL*

Conclusion

- Bleeding is common in cancer, due to cancer per se or due to antineoplastic therapy or antithrombotic therapy.

- Vascular bleeding due to cancer invasion or therapy-related complications is very common.

- Medical causes of clinically relevant bleeding in cancer include the use of antithrombotics, thrombocytopenia, qualitative defect in platelets, coagulation defects and sometimes multifactorial etiologies.

- Management of bleeding requires quick evaluation, arresting bleeding, replacement/supportive therapy and specific management.
Thank you for your attention!