ACQUIRED COAGULATION DISORDERS IN HAEMATOLOGICAL MALIGNANCIES

Professeur Cedric HERMANS, MD, PhD, MRCP (Lon), FRCP (Lon, Edin)
Haemostasis and Thrombosis Unit
Haemophilia Clinic
Division of Haematology
Cliniques Universitaires Saint-Luc
Catholic University of Louvain
1200 Brussels, Belgium
Cedric.hermans@uclouvain.be
THROMBUS FORMATION

1. Platelet plug
   Primary haemostasis

2. Fibrin Formation
   Coagulation cascade

3. Destruction
   Fibrinolysis
**Physiology of Haemostasis**

### Primary Haemostasis
- Vasoconstriction (immediate)
- Platelet adhesion (seconds)
- Platelet aggregation (minutes)

### Secondary Haemostasis
- Activation of coagulation factors
- Fibrin formation (minutes)

### Fibrinolysis
- Activation of fibrinolysis (minutes)
- Clot lysis (hours)

**Vascular injury**

---

*Note: The text is a summary of the stages involved in haemostasis following vascular injury.*
# Evaluation of Haemostasis

<table>
<thead>
<tr>
<th>Vascular Injury</th>
<th>Primary Haemostasis</th>
<th>Secondary Haemostasis</th>
<th>Fibrinolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Platelet count</td>
<td>- PT, APTT</td>
<td>- Euglobulin Lysis Time</td>
</tr>
<tr>
<td></td>
<td>- Bleeding time</td>
<td>- Fibrinogen level</td>
<td>- D-Dimers</td>
</tr>
<tr>
<td></td>
<td>- PFA-100</td>
<td>- Thrombin Time</td>
<td>- RoTEM</td>
</tr>
<tr>
<td></td>
<td>- Platelet aggregaion studies</td>
<td>- INR point-of care</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- RoTEM</td>
<td></td>
</tr>
</tbody>
</table>
# Haemostatic Therapy

## Primary Haemostasis
- Platelet concentrates
- DDAVP (Minirin)
- FVIII-vWF concentrates
- Antifibrinolytics

## Secondary Haemostasis
- Fresh frozen plasma (FFP)
- Clotting factors concentrates
  - Fibrinogen
  - rFVIIa (Novo Seven)
  - PCC (II, VII, IX and X)
  - FVIII, FIX, FXI,...

## Fibrinolysis
- Tranexamic acid

---

**Vascular injury**
CLINICAL ILLUSTRATIONS
FEMALE 40-YEAR-OLD

- Admitted in 03/2007 with Acute LLA-B Phi-
- Hb : 10.5 g/dl
- White cell count : 630/µL
- Platelet count : 9000/µL
- APTT : 26 sec
- Prothrombin Time : 11 sec
- Thrombin Time : 16 sec
- Fibrinogen : 447 mg/dl
- D-Dimers : 6050 ng/ml
- Chemotherapy (GRAAL 2005) (repeated Asparaginase infusions)

- 04/07 Seizure
- Brain MRI : thrombosis superior longitudinal sinus
- APTT : 29 sec
- PT : 16.1 sec
- Thrombin Time : 25 sec
- Fg : 81 mg/dl
- Antithrombin : 50 %

- Treatment :
  - LMWH
  - Antithrombin concentrate

Asparaginase-induced coagulopathy
Female 74-year-old

- Admitted with cardiac failure and peri-orbital hematomas
- Hb : 14.6 g/dl
- WCC : 16450/µL
- Platelet count : 341.000/µL
- Elevated troponin and BNP
- Monoclonal band
- BM : 6 % abnormal plasmocytes
- Cardiac MRI : typical amyloid cardiomyopathy

- APTT, PT and TT : normal
- FX : 75 %
- FVIIIc : > 200 %
- FXI : 172 %
- ELT (euglobulin lysis time) : 60 min (normal > 180)
Female 74-year-old

- Admitted with cardiac failure and peri-orbital hematomas

- Hb: 14.6 g/dl
- WCC: 16450/µL
- Platelet count: 341,000/µL

- Elevated troponin and BNP

- Monoclonal band

- BM: 6% abnormal plasmocytes

- Cardiac MRI: typical amyloid cardiomyopathy

- APTT, PT and TT: normal

- FX: 75%
- FVIIIc: > 200%
- FXI: 172%

- ELT (euglobulin lysis time): 60 min (normal > 180)

Systemic hyperfibrinolysis associated with amyloidosis
**Male 28-year-old**

- Admitted with jaundice (12/2006)
- Hb : 10.4 g/dl
- WCC : 116240 /µL
- Platelets : 16000/µL
- ALL Phi negative
- Chemotherapy (GRAALL 2005)
- Normal clotting tests on admission

- During second consolidation, swelling left superior limb
- US-doppler : thrombosis basilic vein
- Antithrombin level : 43 %
- Fibrinogen : 125 mg/dl
- Asparaginase-induced coagulopathy
- Treatment with AT concentrate and LMWH (therapeutic dose)
MALE 28-YEAR-OLD

- Admitted with jaundice (12/2006)
- Hb : 10.4 g/dl
- WCC : 116240 /µL
- Platelets : 16000/µL
- ALL Phi negative
- Chemotherapy (GRAALL 2005)
- Normal clotting tests on admission
- During second consolidation, swelling left superior limb
- US-doppler : thrombosis basilic vein
- Antithrombin level : 43 %
- Fibrinogen : 125 mg/dl
- Asparaginase-induced coagulopathy
- Treatment with AT concentrate and LMWH (therapeutic dose)

Asparaginase-induced coagulopathy
• Persistent bleeding after prostate biopsy
• Bruising since 4 years
• Post-traumatic extensive haematoma left leg 2 years ago

• Hb : 9.5 g/dL
• APTT : 38 sec
• FVIIIc : 40 % (50-150 sec)

• Von Willebrand factor : 70 % (Antigen) and 5 % (Activity)

• Monoclonal IgM Kappa

• Bone marrow biopsy : CLL
Male 62-year-old

- Persistent bleeding after prostate biopsy
- Bruising since 4 years
- Post-traumatic extensive haematoma left leg 2 years ago

- Hb : 9.5 g/dL
- APTT : 38 sec
- FVIIIc : 40 % (50-150 sec)

- Von Willebrand factor : 70 % (Antigen) and 5 % (Activity)

- Monoclonal IgM Kappa

- Bone marrow biopsy : CLL

Acquired von Willebrand disease
FEMALE 26-YEAR-OLD

- Admitted with diffuse purpura 04/2010
- Hb : 12.3 g/dl
- WCC : 1030 /µL
- Platelets : 117000/µL
- Fibrinogen : 117 mg/dl
- APTT, INR, TT : normal
- D-dimers : 23.950 ng/ml
- AML M3
- Treatment ARA-C, Idarubicin, ATRA
- Normalisation of fibrinogen and D-dimers 1 month after induction
FEMALE 26-YEAR-OLD

- Admitted with diffuse purpura 04/2010
- Hb : 12.3 g/dl
- WCC : 1030 /µL
- Platelets : 117000/µL
- Fibrinogen : 117 mg/dl
- APTT, INR, TT : normal
- D-dimers : 23.950 ng/ml
- AML M3
- Treatment ARA-C, Idarubicin, ATRA
- Normalisation of fibrinogen and D-dimers 1 month after induction
**Male 66-year-old**

- Multiple Myeloma
- Bruising – conjonctival haemorrhage
- Proteinuria 2500 mg/24h
- Bleeding after kidney biopsy
- Amyloidosis
- APTT : 35 sec
- INR : 1.4
- Factor X : 46% (normal value > 70 %)
Mal 66-Year-Old

- Multiple Myeloma
- Bruising – conjonctival haemorrhage
- Proteinuria 2500 mg/24h
- Bleeding after kidney biopsy
- Amyloidosis
- APTT : 35 sec
- INR : 1.4
- Factor X : 46% (normal value > 70 %)

Acquired FX deficiency - amyloidosis
**FEMALE 42-YEAR-OLD**

- Admitted with haematomas, gum bleedings, epistaxis
- Hb : 7 g/dl
- White Cell Count : 440/µL – Blasts
- Platelets : 38000/µL
- AML M3
- APTT : 28 sec
- PT : 16.5 sec
- TT : 25 sec
- Fg : 51 mg/dl
- Treatment : FFP – induction chemotherapy
FEMALE 42-YEAR-OLD

- Admitted with haematomas, gum bleedings, epistaxis
- Hb: 7 g/dl
- White Cell Count: 440/µL – Blasts
- Platelets: 38000/µL

- AML M3

- APTT: 28 sec
- PT: 16.5 sec
- TT: 25 sec
- Fg: 51 mg/dl

- Treatment: FFP – induction chemotherapy
Male 76-year-old

- Multiple myeloma
- Recurrent and severe epistaxis
- APTT: 41 sec
- INR: 1.32
- Thrombin Time: 117 sec
- Reptilase time: normal
- Plasma mixing studies: no correction of the Thrombin Time
- Treatment with plasma exchanges and Novo Seven
M A L E  7 6 - Y E A R - O L D

• Multiple myeloma
• Recurrent and severe epistaxis

• APTT : 41 sec
• INR : 1.32
• Thrombin Time : 117 sec
• Reptilase time : normal

• Plasma mixing studies : no correction of the Thrombin Time

• Treatment with plasma exchanges and Novo Seven

Heparin-like anticoagulant / MM
Bleeding in Myeloid Disorders

- Platelet functional defects
  - Myelodysplasia
  - Polycythemia Rubra Vera (PRV)
  - Essential Thrombocytosis (ET)

- Thrombocytopenia
  - Consumptive coagulopathy
  - Acute leukaemia
Acute Myeloid Leukemia

Thrombocytopenia and platelet dysfunction

• Thrombocytopenia is the most frequent cause of bleeding in patients with AML

• Threshold for platelet transfusion in patients with AML
  – 20,000 /µL in absence of bleeding
  – 50,000/µL in case of bleeding

• Intrinsic platelet functional defects (thrombopathy) are frequent in patients with AML and contribute to bleeding

• Chemotherapy, antibiotics, circulating fibrin degradation products (FDPs) can contribute to platelet dysfunction and failure of platelet plug formation
ACUTE MYELOID LEUKAEMIA

Disseminated intravascular coagulation (DIC) Defibrination syndrome

• Frequent in patients with AML (15%),

• Much more frequent in patients with Acute Promyelocytic Leukaemia (APL – AML M3)

• Mechanisms by which APL cells induce DIC
  – Induction of fibrinolysis (cleavage of plasminogen into plasmin)
  – Release of Tissue Factor (TF)
  – Production of cytokines (IL-1)
  – Release of proteases (Elastase)
SEQUENCE OF EVENTS OCCURRING IN DIC

Thrombotic Event

Bleeding Complication

Underlying disease

Activation of the hemostatic system

Fibrin Formation

Consumption of coagulation factors and platelets

Microvascular thrombosis

Inhibition of fibrinolysis

Preservation of fibrin

Organ failure

Activation of fibrinolysis

Generation of FDP

Hemorrhagic diathesis
Malignant cell-related mechanisms involved in the pathogenesis of disseminated intravascular coagulation in acute leukaemia.
COAGULOPATHY IN PATIENTS WITH AML, PARTICULARLY APL (AML M3)
HYPERFIBRINOLYSIS IN APL (AML-M3)

Coagulopathy in APL: a step forward?

Giuseppe Avvisati  UNIVERSITY CAMPUS BIO-MEDICO

[Diagram of coagulation factors and their interactions in AML.]
Clinical findings and laboratory tests

- Bleeding occurs from diverse sites in patients with acute leukaemia (skin, mucous membranes, GI tract)

- CNS haemorrhage is particularly common in patients with APL

- Risk factors for bleeding
  - Age > 50,
  - Large number of circulating blasts – promyelocytes,
  - Severe anaemia, marked thrombocytopenia

- Patients with all forms of AML should have baseline laboratory tests

- The battery of tests should be repeated at least daily, just before and during chemotherapy or when the clinical picture changes abruptly (e.g. with sepsis)
**Baseline Laboratory Tests in Patients with Acute Leukaemia**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Use(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT, APTT, Fibrinogen</td>
<td>Severity of coagulopathy</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Bleeding time not necessary</td>
</tr>
<tr>
<td>D-Dimer (Euglobulin Lysis Time)</td>
<td>Secondary fibrinolysis</td>
</tr>
<tr>
<td>(Alpha2-antiplasmin)</td>
<td>Secondary fibrinolysis</td>
</tr>
</tbody>
</table>
**Laboratory Tests in Patients with Acute Leukaemia**

<table>
<thead>
<tr>
<th>Severity of DIC</th>
<th>Abnormal Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild DIC</td>
<td>Fibrinogen normal</td>
</tr>
<tr>
<td></td>
<td>APTT shortened</td>
</tr>
<tr>
<td></td>
<td>Minimally elevated D-dimers</td>
</tr>
<tr>
<td>Florid DIC</td>
<td>PT and APPT prolonged</td>
</tr>
<tr>
<td></td>
<td>Reduced Fibrinogen</td>
</tr>
<tr>
<td></td>
<td>AT and protein C reduced</td>
</tr>
<tr>
<td>Systemic fibrinolysis</td>
<td>Very low level of fibrinogen</td>
</tr>
</tbody>
</table>
All-trans-retinoic-acid (ATRA) and APL

- ATRA promotes terminal differentiation of leukemic promyeloyctic cells
- ATRA has raised the complete remission rate of patients with APL to > 90 % along with prompt improvement of the coagulopathy
- ATRA decreases the cellular expression of procoagulant factors such as TF
- Cytokine production is increased after ATRA treatment (implicated in thrombotic complications)
Therapeutic Effects of ATRA in AML-M3

(a) Procoagulant Activity
Decreased

(b) Fibrinolysis
Decreased

(c) Proteases
Unchanged

(d) Cytokines
Increased

**Management of DIC and Defibrination Syndrome**

<table>
<thead>
<tr>
<th><strong>No Active Bleeding</strong></th>
<th><strong>Active Bleeding</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma</td>
<td>Fg level &gt; 125 mg/dl</td>
</tr>
<tr>
<td>Fibrinogen concentrate</td>
<td></td>
</tr>
<tr>
<td>Fg level &gt; 100 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Platelet concentrates</td>
<td>Platelet count &gt; 50,000/μL</td>
</tr>
<tr>
<td>Platelet count &gt; 20,000/μL</td>
<td></td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>Normal APTT</td>
</tr>
<tr>
<td>APTT &lt; 1.5 times control</td>
<td></td>
</tr>
</tbody>
</table>
# Management of DIC and Defibrination Syndrome

<table>
<thead>
<tr>
<th>Other Treatments</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (Low Dose)</td>
<td>Rapid destruction of Fg and platelets</td>
</tr>
<tr>
<td></td>
<td>Thrombotic complications</td>
</tr>
<tr>
<td>Antifibrinolytic agents (Tranexamic acid – Exacyl)</td>
<td>Very short ELT (&lt; 30 min)</td>
</tr>
</tbody>
</table>
**CHRONIC MYELOID DISORDERS**

Myelodysplasia (MDS)

- Bleeding in patients with MDS is almost always due to thrombocytopenia and/or platelet functional defects (PFD)

- A wide spectrum of platelet functional defects have been described in patients with MDS

- Therapeutic options:
  - Platelet transfusion
  - DDAVP (advanced atherosclerosis increases risk of thrombosis)
  - Anti-fibrinolytic agents (refractory oral, nasopharyngeal or GI tract bleeding)
Patients with MPD have an increased risk of bleeding due to platelet dysfunction.

Excessive bleeding is reported in 15% of patients with MPD, most often in patients with ET.

Acquired VWF deficiency should be excluded.

Bleeding is uncommon in patients with CML during the chronic phase.

Management of bleeding in patients with MPD and thrombocytosis involves normalisation of the platelet count.

Fibrinolytic agents should be used with caution in patients with MPD (potentiation of the risk of thrombosis).
LYMPHOPROLIFERATIVE DISORDERS

• Patients with lymphoproliferative disorders are more troubled with excessive bleeding that arterial or venous thrombosis

• Causes of bleeding are multiple:
  – Thrombocytopenia (bone marrow disease / chemotherapy)
  – Acquired platelet, coagulation and fibrinolytic abnormalities have been described
ACUTE LYMPHOCYTIC LEUKAEMIA

DIC

- DIC is frequent in all type of acute lymphocytic leukaemia (ALL)
- Affects 5-10 % of children and adults
- More frequent in patients with T-cell leukaemia
- Higher incidence after initiation of chemotherapy
ACUTE LYMPHOCYTIC LEUKAEMIA
Asparaginase-induced coagulopathy

• L-asparaginase inhibits protein synthesis (coagulation factors and their inhibitors)

• Clinical manifestations:
  – Bleeding may occur a few days after completion of treatment (prolongation of PT, APTT and reduction of Fg)
  – Thrombosis occurs later (2-3 weeks) and has been linked to decreased levels of AT
  – Both bleeding and thrombo-embolic events show a predilection for the central nervous system (CNS): intra-cerebral haemorrhage and cerebral venous thrombosis

• Therapy of L-asparaginase-induced coagulopathy remains controversial
  – FFP
  – Antithrombin concentrate
  – Noy yet known whether this treatment reduces thrombosis of the cerebral veins
CHRONIC LYMPHOCYTIC LEUKEMIA / LYMPHOMA

ITP

- Incidence
  - 10% of patients with CLL
  - 2% of patients with Hodgkin disease
  - Occasionally reported in patients with NHL

- Often associated with activity of HD, may predate diagnosis or appear long after complete remission

- Caused by immune dysregulation in chronic lymphoproliferative diseases

- Standard therapy
  - Corticosteroids
  - Splenectomy
  - IS agents
  - Aggressive treatment of the underlying lymphoproliferative does not always correct the ITP
  - A search for recurrent lymphoma is warranted when ITP develops in patients previously treated for HD
Acquired von willebrand disease

- Acquired VWD is much less common than hereditary VWD

- Blood tests
  - Prolonged bleeding time and PFA-100 (ADP)
  - Reduction of FVIIIc, VWF antigen and activity

- AVWD has been reported in patients with:
  - CLL / B-cell lymphoma / Plasma cell myeloma

- Mechanisms
  - Anti-VWF antibodies (often IgG) that react with the high-molecular-weight multimers
  - Adsorption of plasma VWF on the surface of neoplastic lymphoid cells

- Treatment
  - DDAVP
  - VWF concentrates
  - High dose immunoglobulins
  - Plasma exchanges
  - Splenectomy
ACQUIRED VON WILLEBRAND’S DISEASE

- Malignant diseases
  - Monoclonal gammopathy of unknown significance
  - Multiple Myeloma
  - Non-Hodgkin's lymphoma
  - Chronic lymphocytic leukemia
  - Waldenstrom's macroglobulinemia
  - Essential thrombocythemia
  - Polycythemia vera
  - Chronic myelogenous leukemia
  - Wilms tumor
  - Other carcinomas

- Immunologic disorders
  - Systemic lupus erythematosus
  - Other autoimmune diseases

- Other disorders
  - Hypothyroidism
  - Ventricular septal defect
  - Aortic stenosis
  - Mitral valve prolapse
  - Gastrointestinal angiodyplasia
  - Uremia
  - Hemoglobinopathies

- Drugs and other agents
  - Valproic acid
  - Antibiotics
**Multiple Myeloma and Waldenström Macroglobulinemia**

- Abnormal blood tests are frequent in patients with MM and Waldenstöm Macroglobulinemia

- Severe bleeding is uncommon

- **Bleeding more likely if:**
  - IgA paraproteins
  - Kappa (rather than gamma) light chains
  - High levels of serum proteins
  - Markedly increased serum viscosity

- **Therapy**
  - Treatment of the underlying disorder in order to reduce or eliminate pathologic immunoglobulins and reduce plasma viscosity
  - Intensive plasma-exchanges may be necessary to control bleeding
# Hemostatic Defects Associated with Monoclonal Proteins

<table>
<thead>
<tr>
<th>Effect on Hemostasis</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of platelet aggregation</td>
<td>PFA; Bleeding time</td>
</tr>
<tr>
<td>Inhibition of fibrin polymerization</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>Acquired von Willebrand disease</td>
<td>VWF activity and antigen</td>
</tr>
<tr>
<td>Acquired factor X deficiency</td>
<td>Factor X activity</td>
</tr>
</tbody>
</table>
MULTIPLE MYELOMA AND WALDENSTROM MACROGLOBULINEMIA
Monoclonal proteins with anticoagulant activity

• Thrombin inhibitor
  – High-titer IgG inhibitor with a specific anti-thrombin effect
  – Prolonged thrombin time and reptilase time
  – Plasmapheresis useful to improve coagulation

• Circulating heparin-like anticoagulant
  – Associated with severe bleeding
  – Prolongation of thrombin time but not of reptilase time
  – Treatment: chemotherapy, intensive plasma exchanges, intravenous protamine sulfate
AMYLOIDOSIS

• 10 % of patients with systemic amyloidosis have severe bleeding (easy bruisability)

• Bleeding may result from amyloid infiltration of blood vessels

• Abnormalities of laboratory tests are frequent in patients with amyloidosis but not predictive of bleeding
AMYLOIDOSIS AND ACQUIRED BLEEDING DISORDERS

• Factor X deficiency
  – FX as low as 2-4 % (absorption on amyloid fibrils) has been reported
  – Treatment: splenectomy, chemotherapy

• Chronic systemic fibrinolysis:
  – Absorption of alpha2-antiplasmin on amyloid fibrils,
  – Elevated levels of t-PA, decrease PAI-1 (Vascular damage?)
  – Treatment: antifibrinolytic agents

• Anti-FVIII antibody

• Interference of Bence Jone protein with fibrin polymerization

• RISK of bleeding during liver biopsy should be considered
AMYLOIDOSIS:
BLEEDING LABORATORY WORK-UP

- APTT, PT, TT
- ELT (Euglobulin Lysis Time)
- Alpha-2 antiplasmin
- In a patient with primary hyperfibrinolysis and normal liver function, amyloidosis should be considered
CONCLUSIONS

• Acquired coagulation disorders may complicate many haematological malignancies
  – DIC
  – Acquired von willebrand disease
  – Coagulation factor defect of inhibitor
  – Hyperfibrinolysis

• Coagulation disorders should be rapidly recognised and appropriate treatment initiated
SUGGESTED READINGS


