An Elderly Patient With MDS, Thrombocytopenia, and a Cardiovascular Comorbidity that Requires Anticoagulation or Antiplatelet Therapy

Moshe Mittelman
Tel Aviv Sourasky MC, Tel Aviv University

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Patients
Patient: Mrs. O.S. (63 yr)

- **2012**: Routine CBC - low PLT (60k)
  - Asymptomatic; PMH: Stable IHD; PE – unremarkable
  - Hb 11.4; ANC 2.1k; Dg: LR-MDS

- **Course**:
  - FU only; Gradual PLT decline
  - Minimal SC hematomas

- **2021**:
  - PLT 25k!
  - Atrial fibrillation (AF)
  - Anticoagulation (AC) recommended
Patient: Mr. T.K. (79 yr)

- **2011**: Mild anemia & thrombocytopenia (80k)
  - Dg: LR-MDS
  - PMH: HT; DM; IHD; S/P PCI x 2
- **Course**:
  - Progressive disease
    - Anemia – RBC transfusions; ESA
    - HR-MDS: Aza trials; Transient response
- **2021**:
  - ECOG 0-1; Hb 8; PLT<10k
  - No bleeding
  - RBC & PLT Transfusions
  - Cardiac PCI and TAVI (aortic valve)
  - Clopidogrel? Aspirin?
Patient: Mr. I.R. (73 yr)

- **2015:**
  - Mild anemia (Hb 11.5)
  - Dg: LR-MDS
  - PMH: controlled hypertension
  - Stable disease – lost to follow up

- **2021:**
  - TIA
  - PLT is 42x10^9/L
  - **Aspirin** recommended
The Problem
MDS: Thrombocytopenia

- Low PLT in MDS: **Common**: 40-80%
  - Severe (<30k): 5-20%

- **Bleeding**:
  - Due to: Low PLT; PLT dysfunction
  - Hemorrhagic complications: 3%-53%
    - Death: 13%-24%

- **Other consequences**:
  - Delayed or avoiding anti-MDS treatments
  - **Problem**: AC / APT in CVD

- **Poor prognosis**: AML; Short survival

*References: Mittelman 2000; Bryan 2010; Santini 2015; Basood 2018; Caro 2018; Vijenthira 2019; Wood 2020; Carraway 2020*
EUMDS: Early PLT drop—Poor Prognosis

- **PURPOSE:**
  - Analyze the prognosis of dropping counts
  - 807 LR-MDS pts; Relative ANC, PLT drop (6m)
  - >25% PLT drop - shorter OS (29.2 vs 57.1m)

- **A classifier:**
  - RBC-TD + PLT drop
  - Patients with none vs both criteria;
  - OS 70, 43, 19m

- **Confirmed** with 1610 patients at 10m

- Itzykson R; Blood Advances 2018; ASH 2016
Anticoagulants/Anti platelet treatment (AC/APT) in MDS with Thrombocytopenia – The problem

- Thrombocytopenia common in MDS
- **CVD common** in this (elderly) patient population
- Indication for anticoagulants (AC)
  - or anti-platelet treatment (APT)
- More **complex**:
  - Thrombocytopenia is associated with bleeding
    - **but does not protect against thrombosis**
  - Individual PLT count – poor predictor
  - Other comorbidities; Need for anti-MDS treatment
    - Azacitidine ; Lenalidomide

Leader 2018; 2020; 2021; Basood 2018; Mittelman Lancet Haem 2018; BJH 2021
CAC/APT in Thrombocytopenic MDS – Various Clinical Settings

- **Anticoagulants (AC)**
  - Treatment: Temporary (acute VTE)
  - Prevention - chronic
    - CAF; Stroke prevention
    - Recurrent DVT; TIA/stroke

- **Anti platelet treatment (APT)**
  - Cardiac (long term)
    - Acute MI; PCI; Procedures

- **Agents:**
  - AC; APT - several

Leader A; Crit Rev Oncol/Hem 2018; 132:76
Possible Solutions
AC/APT in Thrombocytopenic MDS – Possible Solutions

- Ignore thrombocytopenia – take the risk – full AC/APT
- **Avoid** AC/APT: Temporary ? Till PLT>50k
- PLT transfusions
  - Raise PLT threshold (40-50k)
- **Modified** dose AC/APT
  - Reduced; How much ? Temporary; Intermittent
- Thrombomimetics (TPO-RA)
- Change anti-MDS treatment
  - Or CV treatment (Watchman)
- Anti-fibrinolytics – minimize bleeding

*Leader A, 2018; 2020; 2021*
MDS with Thrombocytopenia: What Can We Do?
LR-MDS: PLT Transfusions

- Indication – in active **bleeding** (immediate)
  - No evidence for prophylactic
- PLT transfusion – per **local guidelines**
  - When PLT < 10k ??
- Consider “thrombostatics”
  - Tranexamic acid
  - Anti-fibrinolytic: Hexakapron

Malouf R, Cochrane Database Syst Rev 2018 May 14; Vijenthira 2019
Bowen D, Mittelman M, ELN-EUMDS Guidelines 2019 (on line); Carraway 2020
Thrombomimetics ? Yes

- Thrombopoietin receptor agonists (TPO-RA)
  - **Romiplostim** *(Nplate®)*; **Eltrombopag** *(Revolade®)*
- Both drugs (mono / combo)
  - LR-MDS and HR-MDS
- **Effects** (40-50%):
  - Increase PLT count
  - Reduce PLT transfusions
  - Decrease clinically significant bleeding
  - Improve QoL
- Reasonable tolerance

Kantarjian 2010; Giagounidis 2014; Fenaux 2017; Oliva 2018; Kehelif AJH 2019
Mittelman 2018; 2019; Dickinson 2018; Carraway 2020; Vicente Haematol 2020
### Fewer Clinically Relevant Thrombocytopenic Events in Eltrombopag Patients

<table>
<thead>
<tr>
<th></th>
<th>Eltrombopag (N=98)</th>
<th>Placebo (N=47)</th>
<th>Odds ratio [95% CI]</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>Mean CRTE (Weeks 5–12)</td>
<td>54% [43-64]</td>
<td>69% [57-80]</td>
<td>0.202 [0.047-0.867]</td>
<td>0.0315</td>
</tr>
</tbody>
</table>

**CRTE Analysis Over Time; Generalized Linear Mixed Model**

*Graph showing CRTE analysis over time for Placebo and Eltrombopag groups.*

*Source: Mittelman M et al, Lancet Haematol 2018*
Thrombomimetics ? Caution/ Concerns

- Two “negative” trials
  - Early terminated!
- **Romiplostim** trial:
  - LR-MDS
  - Elt 58 wk: AML 6% (ROM) vs 4.9%
    - Overall survival - similar
- **SUPPORT**:
  - HR-MDS; Aza + Elt vs Aza
  - Futile – No effect; More AML
- **Development – stopped!**

*Giagounidis 2014; Dickinson 2018*
TPO RA – Still Embargo?

- "Negative" trials
  - ROM; SUPPORT
- "Positive" / Safe
  - Others (both agents; LR-MDS)
  - Long-term FU – safe (ASPIRE III)
  - Real-life (GFM/ Elt) – Safe!
- Meta-analysis (n=2):
  - No excess mortality!
- Conclusion?
  - My personal: Time to lift the embargo

Fenaux 2017; Dodilet 2017; Oliva 2018; Kantarjian 2018; Mittelman ASH 2019
Mittelman 2018; 2019; Meng 2020; Comont 2021; Mittelman BJH 2021
Thrombomimetics on the Way

- Recombinant human thrombopoietin (rhTPO)
  - rhTPO – 15ku/d x7d /m x 3m
  - LR-MDS on stanozolol +/- rhTPO (20 vs 15)
- Results
  - PLT rise; Fewer Transfusions
  - HI; no PR/CR; No difference in ORR / CR
  - No safety concern after 12m
- Avatrombopag:
  - Peri-procedural for neurosurgical interventions
  - In chronic liver disease

Yang Y Font Oncol 2021;11:721764; Ming Y, Bl Ad 2020; 18 (Sept)
Lessons: AC/APT in Cancer Patients with Thrombocytopenia
AC in Patients with Cancer associated VTE and Thrombocytopenia

- **Objective**: Retrospective: VTE management
- **Methods**:
  - Cohort: **Cancer + acute VTE + thrombocytopenia**
  - Regional cancer Ctr; Edmonton, Alberta; 2005-2011
  - **Endpoints**: rec VTE; Bleeding; 3m from VTE
- **Results**:
  - Total n=74 patients
  - 23.0 % - no Rx; 40.5% full AC; 36.5 % partial AC
  - **Outcomes**: 31.1 % rec VTE; 17.6 % bleeding (4.1 % major)
- **Conclusion**:
  - Heterogenous treatment; Frequent complications
  - **No practical recommendation**

AC in Transplanted Patients with prior VTE

- **Objective:**
  - Retrospective comparison:
    - Outcome of continuing vs (temporary) D/C of AC, in
      - Transplanted (allo + auto) and prior VTE

- **Results (30d):**
  - 13% of HCT
  - Rec VTE – similar (4 vs 3%)
  - Bleeding – more with AC (41% vs 31%)

- **Conclusion:**
  - **Temporary D/C of AC** - till PLT rise
AC Modified Dose in Cancer with Thrombocytopenia?

- **Background**: Reduced dose? Short time? Interrupted?
- **Aim**: Prospective comparison: Full vs Modified AC
- **Patients**:
  - Active cancer + Acute VTE + PLT < 100K
- **Results (60d)**:
  - Total n=121; 62% Full AC; 27% Modified; 11% No AC
  - Major bleeding: Full 12.8%; Mod 6.6%
  - Rec VTE: Full 5.6%; Mod 0%
- **Conclusion**: prefer modified AC - safe

Carney BJ; Bl Ad 2021
The Bleeding Risk with AC in AF & Thrombocytopenia

- A retrospective study (Israel; Netherland)
- **Methods**: Patients with hematologic neoplasms
  - AC for AF + PLT<50k; FU 30d
- **Results**:
  - n=61; 69% on AC at index day
  - < 65yr + new AF – tend to withhold AC
  - **AC associated with bleeding 17% vs 5.3%**
  - TE – similar 2.4% vs 5.3%
  - High mortality – 45% !!
- **Conclusion**:
  - The bleeding risk outweigh the risk of TE !

*Livneh N; J Thromb Thrombolysis 2021; 52: 590*
Is Baseline thrombocytopenia associated with poor outcome in PCI?

- **Aim**: Effect of thrombocytopenia on PCI outcomes
- **Setup**: 3 studies; PCI; Japan; 19,353 patients
- **Methods**:
  - Baseline Thrombocytopenia:
    - **Mild** 100-150x10⁹/L; **Moderate** 50-100k; **Severe** < 50k
  - **Endpoints** 3yr: Ischemia (MI/stroke); Bleeding (thrombolytic use)
- **Results**:
  - 2,590 patients (13.4%) with baseline thrombocytopenia
  - 1.5% moderate/severe; 11.9% mild
  - **Ischemia** : Common as in no thrombocytopenia, HR 1.07; 0.93 !!
  - More bleeding: HR 2.35; HR 1.20
  - Higher Mortality: HR 2.34; HR 1.26
- **Conclusion**: In thrombocytopenia - Bleeding risk; High mortality

*Ito* S. Am J Cardiol 2018;121:1304
Aspirin Is Associated with Improved Survival in Hematologic Neoplasms (HN) + Severe Thrombocytopenia + Acute MI

- **Aim**: Is aspirin safe (bleeding) and useful 7d of acute MI?
- **Methods**:
  - Retrospective records review; MSKKCC; 2205-2014
  - **Patients**: HN + Acute MI + PLT<50k (sTP)
- **Results**.
  - n=118 with HN + Acute MI; 49% sTP; 43% got aspirin
  - 1y OS: Shorter for for sTP – 23% vs 50%
  - 1y OS: *With aspirin better* - 32% vs 13%
  - No major bleeding with aspirin
- **Conclusion**.
  - Aspirin associated with improved OS in HM+MI+ sTP ; Safe
- **Implications**: Aspirin can be given within 7d of acute MI

Feher A, The Oncologist 2017; 22; 213
Approach to Cancer Patients with Acute Coronary S. + Thrombocytopenia (Rev)

- **CABG**: Postpone 2-6 wk; PLT>50k
- **Thrombocytopenia**: < 100k
- Thrombocytopenia and thrombophilia often coexist
- **7d survival**: better with aspirin; no severe bleeding
- **PCI**: AC/APT dose based on PLT
  - PCI safe when PLT 40-50 k/μL (w/o thrombophilia)
  - **If PLT** <50k: Unfractionated Heparin 30-50u/Kg
  - **If PLT**>50k: UFH dose 50-70 U/kg
- **ACT monitoring crucial**

Rudmilov J; J Clin Med 2020; 9(12):3926
Impact of Thrombocytopenia in Patients With Atrial Fibrillation Undergoing Left Atrial Appendage Occlusion

**Objectives:** Outcomes of LA appendage occlusion (LAAO)

**Methods:** LAAO (2016-2018) in AF + TP (PLT<100k)
- Compared with a propensity-matched cohort: LAAO-no TP

**Results** (n=32)
- Similar stroke (0 vs. 3.1%); TE (0 vs. 0.6%)
- Similar Device-related thrombus (3.1 vs. 2.5%)
- More bleeding in TP
- In both groups: TE and stroke – reduced

**Conclusion:** LAAO (Watchman) safe and effective
- Caution: Bleeding

Zhang X, Front Cardiovasc Med 2021; April 9; 8: 603501
Direct oral anticoagulants (DOAC) in patients with hematologic neoplasms (HN)

- **Aim**: DOAC efficacy and safety
- **Methods**: HN + DOAC for AF or VTE
- **Results**: n=135 patients
  - 104/135 on anticancer therapy
  - No thrombotic or major bleeding
  - Minor bleedings in 10 patients
    - More in MDS
  - Plasma levels helped in dose adjustment
- **Conclusion**:
  - DOACs effective and safe in HN

*Serrao A, Hematol Oncol 2020; 38: 589*
Dual anti-platelet therapy in PCI with thrombocytopenia

- **Aim:** Study PCI outcomes in thrombocytopenia and DAPT
- **Methods:** Meta analysis; compare w/wo Low PLT
  - Endpoints: bleeding, stent thrombosis, stroke, other CV
- **Results:**
  - 8 studies; 119,000 patients; 38,000 with low PLT
  - More bleeding with low PLT
  - Higher mortality with low PLT
  - Similar thrombosis
- **Conclusions:**
  - DAPT – risk in PCI with thrombocytopenia.

AC/APT in Thrombocytopenic MDS - Summary

• The literature in 2021:
  • Little info; (not MDS)
  • More reviews than originals
  • Heterogenous (all cancers, all AC, extrapolation, small #...)
  • Retrospective

• More questions than answers

• Conclusions:
  • PLT > 50k – safe
  • Thrombotic risk lower in:
    • Non-acute VTE; Catheter-related VTE; AF (LR)
  • Bleeding risk > thrombotic
ACRE/APT in Thrombocytopenic MDS - Recommendations

- Consider indication
  - Risk: Thrombotic vs bleeding
    - benefit/ risk ratio

- Consider:
  - Patient preference
  - Age; MDS status
  - Try a temporary treatment duration

- Clinical & personal judgment

- Apologize for being non-practical enough

Leader A; Thromb Res. 2020 Jul;191 Suppl 1:S68-S73
Leader A; J clin Med 2021; 10: 1169
AC/APT in Thrombocytopenic MDS - Future

- Effective / safe agents
- We need:
  - Prospective trials
  - Large numbers
  - Focus on a homogenous patient population
    - A single indication; A single drug...
- Will require:
  - Collaboration
    - International
    - Multi disciplinary: hem/onco, coag, cardiol, neurol...
  - New tools – AI
From The Tel Aviv Sourasky Medical Center