

# Predictive Factors of Fatal Bleeding in Acute Promyelocytic Leukemia

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April 2018



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# Disclosure

- I received salary support from Janssen Pharmaceuticals.



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# Overview

- **Epidemiology of bleeding in APL**
- **Pathophysiology of the coagulopathy of APL**
- **Predictors of hemorrhagic death**
  - Clinical usefulness
  - How to identify valid predictors
  - Evidence base
- **Future avenues**



# Epidemiology



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# Acute Promyelocytic Leukemia

- APL is an uncommon myeloid neoplasm characterized by the t(15;17) rearrangement
- ATRA has been a cornerstone of treatment for three decades now
  - Induces terminal differentiation of leukemic blasts
- Bleeding is a common presenting feature of the disease



# Bleeding in APL

- In multicenter trials of APL treatment, about 5% of patients die of hemorrhage
  - Probably more in the “community” setting
- Hemorrhagic deaths (HD's) account for most of the induction mortality
- No improvement in these figures since ATRA entered mainstream use



# Coagulopathy



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# The Coagulopathy of APL

- Coagulation testing is usually abnormal in newly diagnosed cases of APL
  - Prolonged PT and aPTT, decreased platelet count and fibrinogen
- The exact mechanisms and their respective contributions to the bleeding manifestations have not been well delineated
- The most likely processes include:
  - Primary hyperfibrinolysis
  - Disseminated intravascular coagulation (DIC)





# The Coagulopathy of APL

- **Primary hyperfibrinolysis:**
  - Annexin II is present at the surface of APL blasts
  - tPA binds to and is potentiated by Annexin II
  - Plasminogen is converted to plasmin by tPA, leading to depletion of fibrinogen and destruction of fibrin clots at bleeding sites



# The Coagulopathy of APL

- **Disseminated intravascular coagulation:**
  - APL blasts contain large amounts of tissue factor (TF)
  - TF complexes with factor VII, leading to its activation
  - TF/VIIa activates factors IX and X, leading to thrombin generation and conversion of fibrinogen to fibrin
  - Platelets are also consumed in the process, leading to decreased capacity to form a thrombus at sites of injury



# Predictors of Hemorrhagic Death



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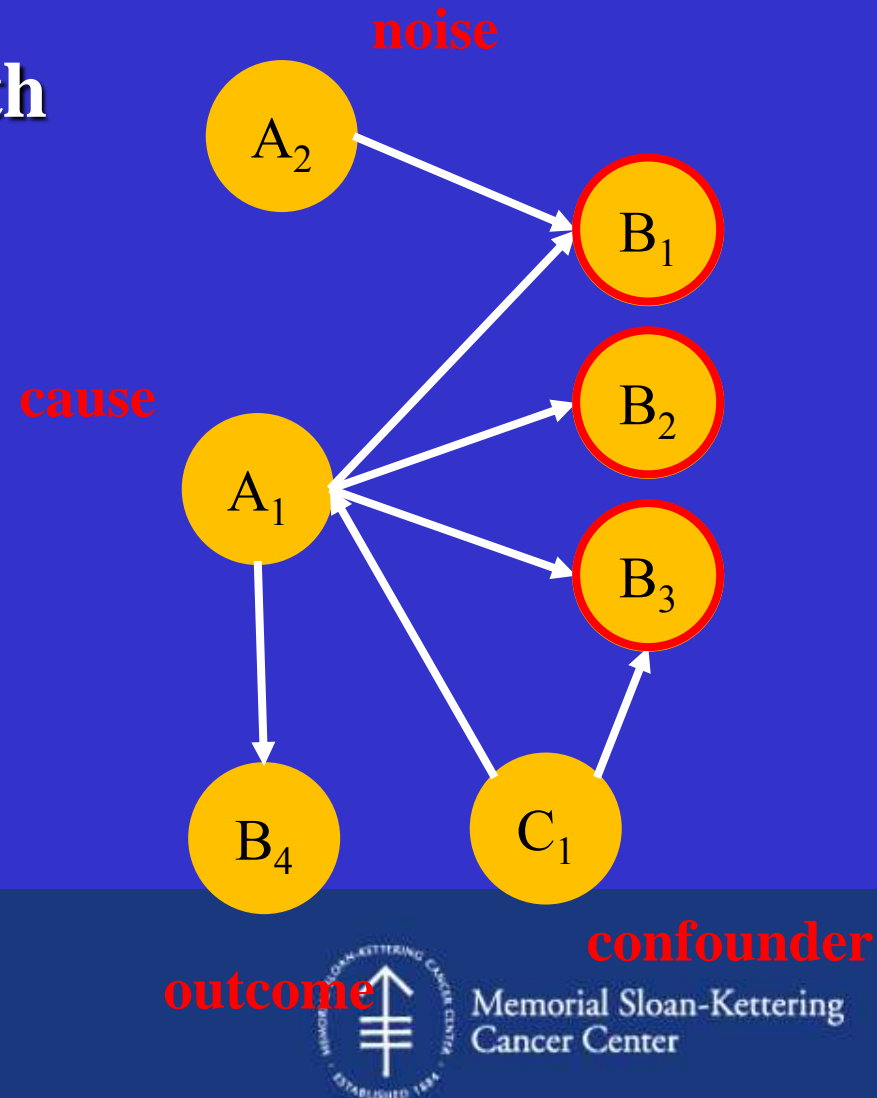
# Potential Clinical Usefulness of Predictors

- Why should we attempt to predict the risk of HD in APL?
  - Developing a reliable prediction rule would allow stratification of newly diagnosed patients
  - High-risk individuals could benefit from dedicated interventions
  - Decreasing the rates of HD could make a substantial dent in induction mortality for APL



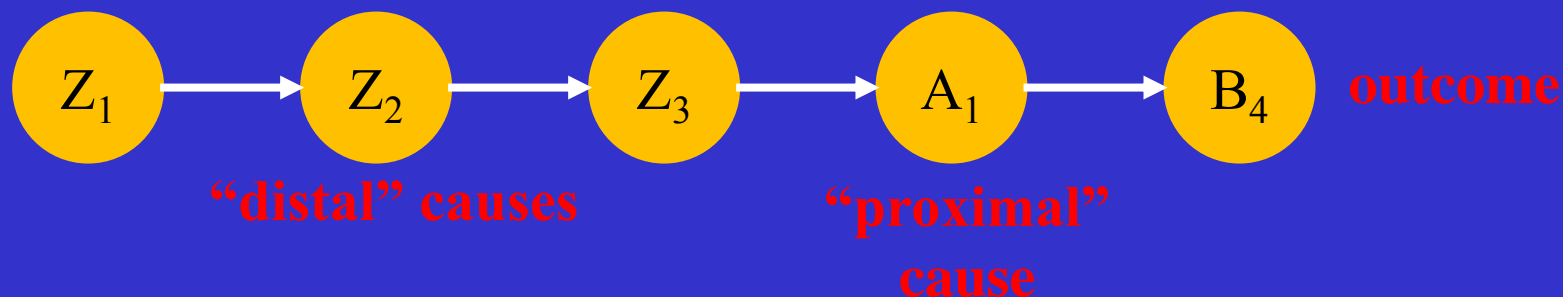
# What Makes a Good Predictor?

- Strongly correlated with the outcome
  - “dose effect”
- Directly reflects causality
  - Not mandatory
- Independent
  - Pick only one of several redundant, “collinear” factors



# What Makes a Good Predictor?

- Prior knowledge is often helpful when attempting to identify predictors
  - The APL blast is arguably early in the causation chain:

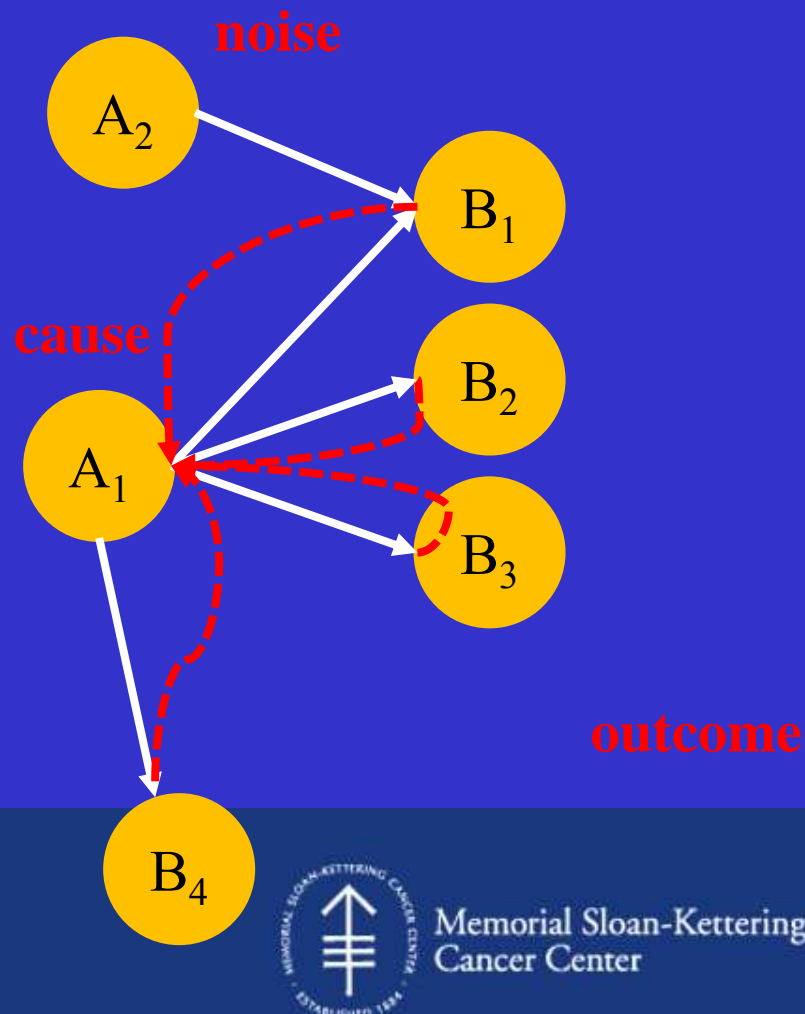


- Basic science of the coagulopathy of APL is not well developed



# What Makes a Good Predictor?

- Commonly performed lab assays are crude predictors:
  - Not in the causal chain
  - Collinear
  - Susceptible to noise
  - Subject to bias from administration of blood products based on threshold lab values



# Limits of Current Evidence

- All data on predictors of HD in APL are retrospective
  - Difficult to address sources of bias (e.g. blood product administration)
  - Limited information on predictors is available (e.g.: only basic tests of hemostasis)





# Evidence Base

- Predictors with published data:
  - White blood cell (WBC) count
  - Peripheral blood (PB) blast count
  - Platelet count
  - Prothrombin time (PT)
  - Activated partial thromboplastin time (aPTT)
  - Fibrinogen
  - Performance status (PS)



# Evidence Base

| Author, Year                    | Number of Patients | Endpoint                                      | Significant Predictors of Bleeding Risk                          |
|---------------------------------|--------------------|-----------------------------------------------|------------------------------------------------------------------|
| Abla <i>et al</i> , 2017        | 683                | Thrombo-hemorrhagic early death               | WBC count, PB blast count, morphological subtype, ethnicity, BMI |
| Mantha <i>et al</i> , 2017      | 995                | Hemorrhagic early death                       | WBC count, PB blast count, ECOG PS                               |
| Mitrovic <i>et al</i> , 2013    | 56                 | Hemorrhagic early death                       | WBC count, ECOG PS, fibrinogen, PT, ISTH DIC score               |
| Chang <i>et al</i> , 2012       | 116                | WHO grade 3 or 4 bleeding                     | WBC count, PT, PTT                                               |
|                                 |                    | WHO grade 4 bleeding                          | WBC count, PT, PTT                                               |
| Kim <i>et al</i> , 2011         | 90                 | Significant bleeding (defined by the authors) | Platelet count, LDH, fibrinogen, D-dimers                        |
|                                 |                    | Hemorrhagic death                             | Platelet count, LDH, fibrinogen                                  |
| De la Serna <i>et al</i> , 2008 | 732                | Hemorrhagic induction death                   | Age, creatinine, WBC count, PB blast count, coagulopathy         |
| Yanada <i>et al</i> , 2007      | 279                | Severe hemorrhage (defined by the authors)    | Fibrinogen, WBC count, ECOG PS                                   |
| Dally <i>et al</i> , 2005       | 34                 | Severe bleeding (defined by the authors)      | PT, WBC count                                                    |
| Higuchi <i>et al</i> , 1997     | 19                 | Hemorrhagic early death                       | Fibrinogen                                                       |



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# Determinants of fatal bleeding during induction therapy for acute promyelocytic leukemia in the ATRA era<sup>1</sup>

- 995 patients from 5 trials:
  - ALLG APML3
  - ALLG APML4
  - CALGB 9710
  - ECOG-ACRIN E2491
  - SWOG S0521
- Endpoint: hemorrhagic death at 30 days of induction start



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# Distribution of Predictor Values

|                                         |                   | Trial            |                  |                  |                  |                  | p-value |
|-----------------------------------------|-------------------|------------------|------------------|------------------|------------------|------------------|---------|
|                                         |                   | APML3<br>(N=101) | APML4<br>(N=124) | C9710<br>(N=481) | E2491<br>(N=198) | S0521<br>(N=105) |         |
| WBC Count<br>(1000/mcL)                 | Median<br>(range) | 2.4 (0.4-109)    | 2.4 (0.1-85.8)   | 2.3 (0.2-139)    | 2.2 (0.3-550)    | 1.4 (0.3-12.4)   | <.001   |
| Peripheral<br>Blast Count<br>(1000/mcL) | Median<br>(range) | 0.3 (0.0-79.9)   | 0.6 (0.0-81.0)   | 0.1 (0.0-134)    | 0.2 (0.0-303)    | 0.0 (0.0-11.6)   | <.001   |
| Platelet<br>Count<br>(1000/mcL)         | Median<br>(range) | 24.0 (4.0-180)   | 22.0 (2.0-173)   | 30.0 (1.0-232)   | 36.0 (5.0-587)   | 35.0 (5.0-237)   | <.001   |
| ECOG<br>Performance<br>Status           | 0-2               | 97 (96)          | 118 (95.2)       | 446 (94.7)       | 178 (90.8)       | 102 (97.1)       | 0.19    |
|                                         | 3-4               | 4 (4)            | 6 (4.8)          | 25 (5.3)         | 18 (9.2)         | 3 (2.9)          |         |



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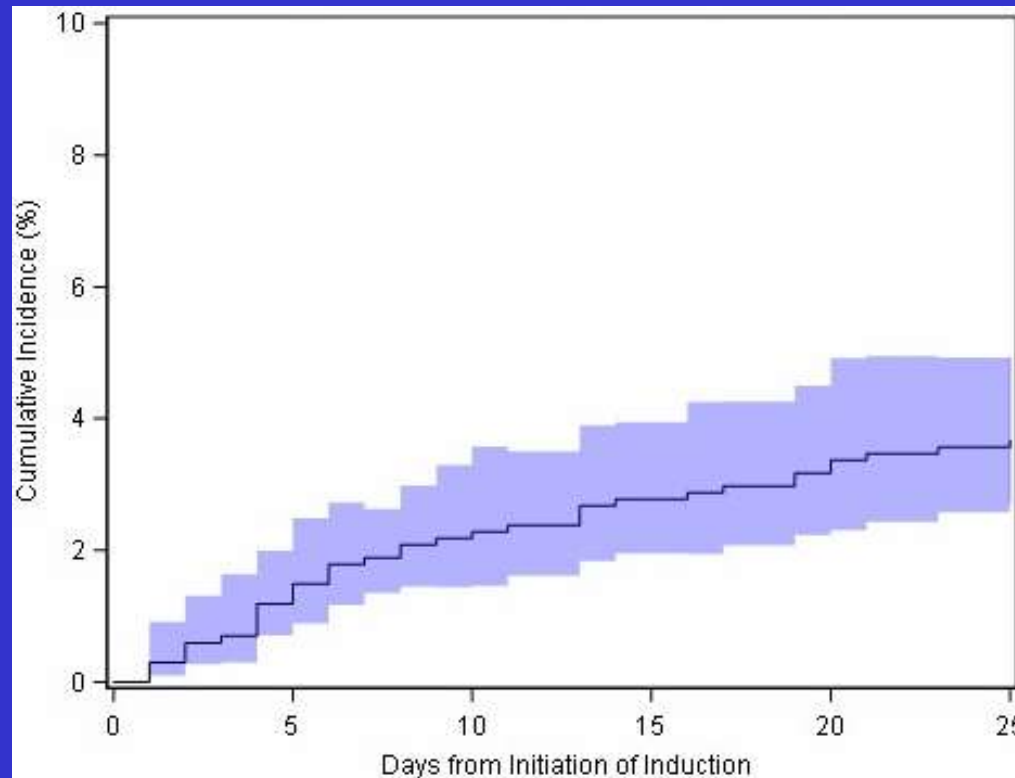
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| PT (seconds)      | Median<br>(range) | 15.5 (11.1-306)  | 16.0 (10.0-25.0) | 14.7 (0.9-82.4)  | 13.8 (10.3-71.0) | NA               | <.001   |
| aPTT<br>(Seconds) | Median<br>(range) | 29.0 (21.0-50.0) | 28.5 (20.0-56.0) | 28.0 (17.0-363)  | 27.2 (17.7-81.0) | NA               | 0.005   |
| Fibrinogen        | Median<br>(range) | 180 (40.0-570)   | 170 (50.0-630)   | 35.0 (14.0-370)  | 187 (51.0-660)   | NA               | <.001   |



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# Cumulative Incidence of Hemorrhagic Death



- There were 37 cases of early HD (cumulative incidence=3.7%, 95% CI=2.6-5%)



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# Univariate Cox PH Models

|                                    |                        | N Included (#HD) | HR   | p-value |
|------------------------------------|------------------------|------------------|------|---------|
| Age (years)*                       |                        | 1009 (37)        | 1.07 | 0.463   |
| PT (seconds)*                      |                        | 837 (33)         | 1.07 | 0.054   |
| WBC Count* (1000/mcL)*             |                        | 999 (37)         | 1.07 | <.001   |
| WBC Count (grouped)                | High Risk( $\geq 20$ ) | 129 (16)         | 5.49 | <.001   |
|                                    | Low Risk(<20)          | 870 (21)         | REF  |         |
| Platelet Count* (1000/mcL)         |                        | 999 (37)         | 0.91 | 0.107   |
| Platelet Count (grouped)           | High Risk(<30)         | 484 (21)         | 1.41 | 0.297   |
|                                    | Low Risk( $\geq 30$ )  | 515 (16)         | REF  |         |
| Peripheral Blast Count* (1000/mcL) |                        | 870 (34)         | 1.12 | <.001   |
| PTT* (seconds)                     |                        | 882 (37)         | 0.95 | 0.627   |
| Fibrinogen (mg/dL)                 |                        | 861 (35)         | 1.00 | 0.689   |
| Hemoglobin(g/dL)*                  |                        | 996 (37)         | 0.54 | 0.464   |
| Creatinine Clearance* (ml/min)     |                        | 869 (36)         | 0.96 | 0.495   |
| ECOG Performance Status            | Poor(3-4)              | 56 (5)           | 2.76 | 0.035   |
|                                    | Good(0-2)              | 939 (32)         | REF  |         |
| FAB Classification                 | M3v                    | 125 (8)          | 2.28 | 0.054   |
|                                    | M3                     | 592 (17)         | REF  |         |

\*Increases of 10 units.



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# Univariate Cox PH Models

|                                    |                        | N Included (#HD) | HR   | p-value         |
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# Multivariate Cox PH Regression

|                         |                        | HR   | 95% CI     | p-value |
|-------------------------|------------------------|------|------------|---------|
| WBC Count (grouped)     | High Risk( $\geq 20$ ) | 5.20 | 2.70-10.02 | <0.01   |
|                         | Low Risk(<20)          | REF  |            |         |
| ECOG Performance Status | Poor(3-4)              | 2.17 | 0.84-5.62  | 0.11    |
|                         | Good(0-2)              | REF  |            |         |

- PB blast count not included due to collinearity with WBC



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# Predictors of thrombohemorrhagic early death in children and adolescents with t(15;17)-positive acute promyelocytic leukemia treated with ATRA and chemotherapy.

- 683 children from 9 study groups:
  - AIEOP
  - PETHEMA
  - BFM
  - CALGB
  - (...)
- Main outcome: thrombohemorrhagic death <30 days of presentation



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# Distribution of Predictors

| Characteristic                                    |                | Value            |
|---------------------------------------------------|----------------|------------------|
| Age (years)                                       | Median (range) | 12.7 (0.4-19.0)  |
| WBC Count (10,000/mcL)                            | Median (range) | 3.8 (0.2-339.2)  |
|                                                   | N >10,000 (%)  | 217 (32)         |
| Median % PB blast count (range)                   |                | 35 (0-100)       |
| Median platelet count x10 <sup>9</sup> /L (range) |                | 23 (1-53)        |
| N with M3v variant (%)                            |                | 111 (16.6%)      |
| Median Body Mass Index (range)                    |                | 19.6 (10.9-49.7) |



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# Event Counts

- There were 25 thrombohemorrhagic ED events:
  - 19 CNS bleeds
  - 4 pulmonary bleeds
  - 2 CNS thrombotic episodes

(3.4% of patients died of bleeding)



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# Multivariate Cox PH Regression

|                     | HR   | 95% CI     | p-value |
|---------------------|------|------------|---------|
| Elevated WBC Count* | 3.97 | 1.50-10.52 | <0.01   |
| M3v                 | 2.13 | 0.83-5.47  | 0.11    |
| Increased BMI §     | 2.70 | 1.11-6.59  | 0.03    |

- \*WBC>10,000
- §≥95<sup>th</sup> percentile



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# Overview of Available Evidence Base



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# WBC Count

- **WBC>10,000/mcL predicts lower relapse-free survival<sup>1</sup>**
- **A threshold of 10,000-20,000/mcL predicts early hemorrhagic death in two large studies<sup>2-3</sup>**
  - **Independent predictor of severe bleeding in two other series<sup>4-5</sup>**

1. Sanz MA *et al*, Blood 2000.
2. Abela O *et al*, Ann Hematol 2017.
3. Mantha S *et al*, Blood 2017.
4. Yanada, M *et al*, Eur J Haematol 2007.
5. Dally N *et al*, Thromb Res 2005.



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# PB Blast Count

- PB blast count is strongly correlated with WBC
  - Predictor of early hemorrhagic death in univariate<sup>1,2</sup> and multivariate analysis<sup>3</sup>
  - Collinearity will affect computation of regression coefficients
  - Best is to only use one of the two variables

1. Abala O *et al*, Ann Hematol 2017.
2. Mantha S *et al*, Blood 2017.
3. De la Serna *et al*, Blood 2008.



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# Platelet Count

- Platelet count will be affected by DIC and marrow replacement by blasts
- Thrombocytopenia will cause spontaneous bleeding usually only below 20,000/mcL
  - Transfusion therapy is a source of bias
- Platelet count has not emerged as a good predictor of severe bleeding
  - Only reported in one small series<sup>1</sup>



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# Prothrombin Time

- PT reflects levels of fibrinogen along with factors II, V, VII and X
  - Affected by DIC and primary hyperfibrinolysis
- PT was not found to be a significant predictor of severe bleeding in multivariate analysis
  - Univariate predictor in three small series

1. Mitrovic M *et al*, Med Oncol 2013.
2. Chang H *et al*, Eur J Haematol 2012.
3. Dally N *et al*, Thromb Res 2005.



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# Activated Partial Thromboplastin Time

- aPTT reflects levels of fibrinogen along with factors II, V, VIII, IX, X and XI
  - Affected by DIC and primary hyperfibrinolysis
- aPTT does not seem to be useful for predicting severe bleeding in APL
  - Only reported as a univariate predictor in one small study<sup>1</sup>



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# Fibrinogen

- Both acute DIC and primary hyperfibrinolysis will depress fibrinogen levels
  - Plasmin is not perfectly selective
- Fibrinogen level is used as a transfusion trigger for cryoprecipitate



# Fibrinogen

- **Fibrinogen was shown to be a predictor of severe bleeding in four studies**
  - Multivariate in two studies<sup>1,2</sup>
  - Univariate only in two other instances<sup>3,4</sup>

1. Kim DY *et al*, Leuk Res 2011.
2. Yanada, M *et al*, Eur J Haematol 2007.
3. Mitrovic M *et al*, Med Oncol 2013.
4. Higuchi *et al*, Hematol Oncol 1997.



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# Performance Status

- PS encapsulates multiple pieces of information
- ECOG PS is a predictor of severe bleeding in APL induction
  - Found to be an independent predictor in one study<sup>1</sup>
  - Univariate predictor in two studies<sup>2,3</sup>

1. Yanada, M *et al*, Eur J Haematol 2007.
2. Mitrovic M *et al*, Med Oncol 2013.
3. Mantha S *et al*, Blood 2017.



# Other Variables

- Microgranular variant (M3v)<sup>1</sup>
- Body mass index (BMI)<sup>1</sup>
- Ethnic group<sup>1</sup>
- Age<sup>2</sup>
- Creatinine<sup>2</sup>

1. Abal O *et al*, Ann Hematol 2017.
2. De la Serna *et al*, Blood 2008.



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# Future Avenues



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# Moving Forward

- **Laboratory hemostatic testing built-in future RCT's of APL induction would allow capture of better data:**
  - Investigational assays
  - Uniform collection
  - Centralized testing
  - Adjust for transfusion therapy
- **If a reliable model can be devised, subsequent trials could implement risk-adapted therapy**



# Summary

- The most consistent predictor of early hemorrhagic death during APL induction is the total WBC count
- Primary hyperfibrinolysis appears to be the main pathophysiological mechanism
- We are still far from risk-adjusted therapy
  - Ultimate aim is to decrease hemorrhagic mortality





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