COMPLICANZE EMORRAGICHE E TROMBOTICHE IN ONCOLOGIA: DIAGNOSI E TERAPIA

Milano, 26-26 novembre 2008

Fondazione IRCCS Istituto Tumori

Le piastrinopenie in oncologia: cause, diagnosi e terapia

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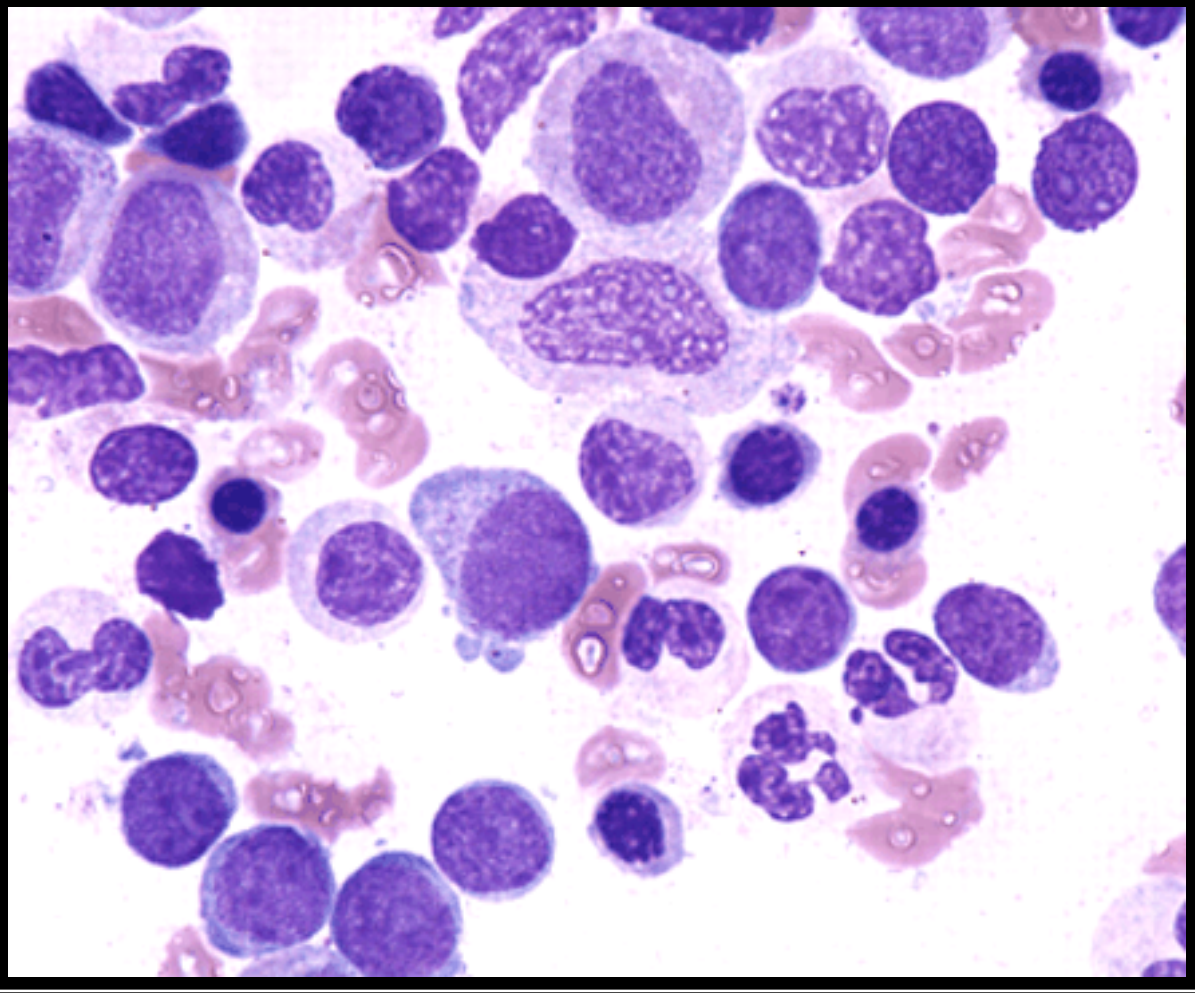
Thrombocytopenia and cancer: multiple origins

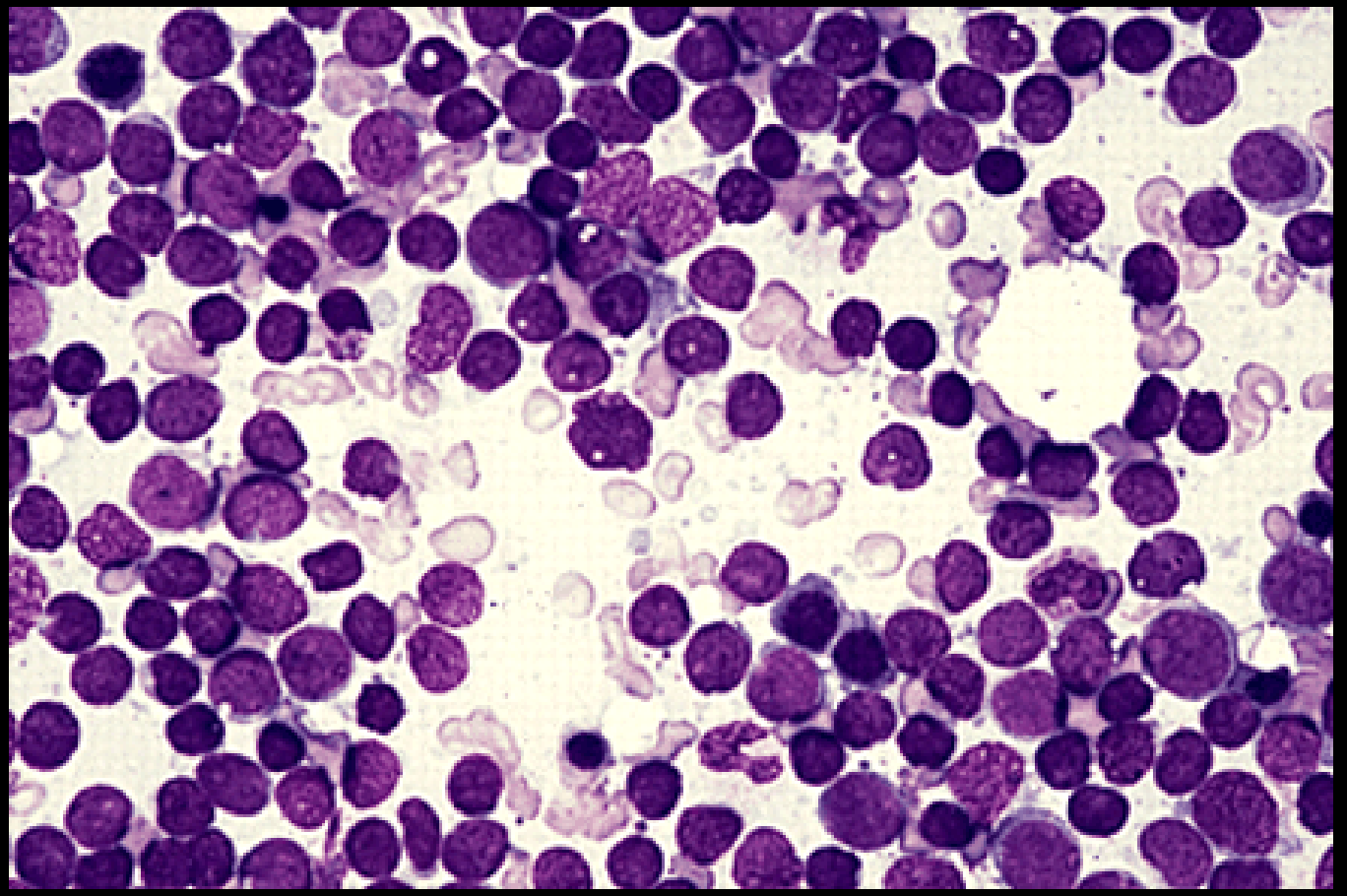
1. Reduced platelet production

- Primary bone marrow disease (leukemia,myeloma, advanced lymphoma)
- Solid tumors with bone marrow metastases
- Paraneoplastic syndromes (rare)

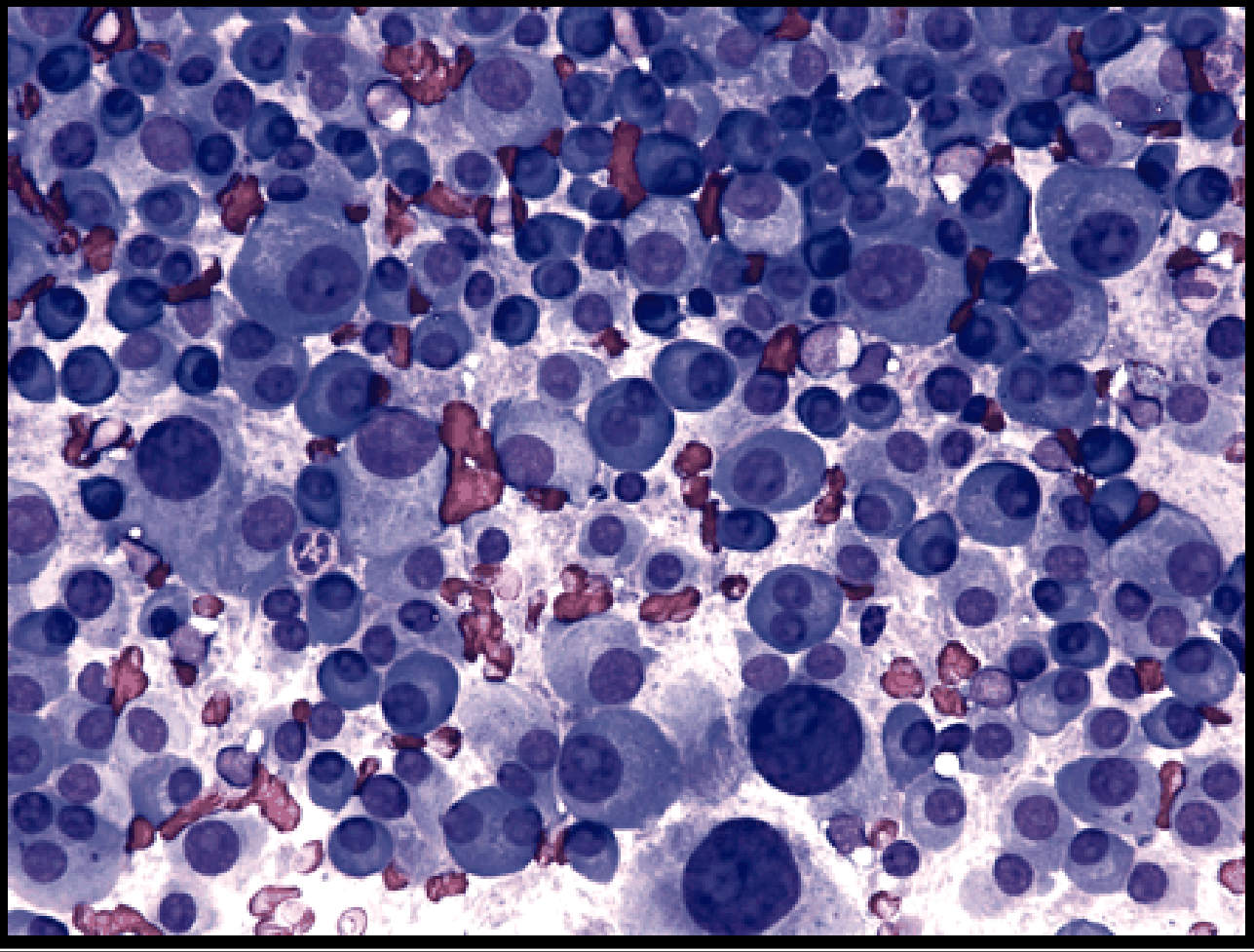
AML



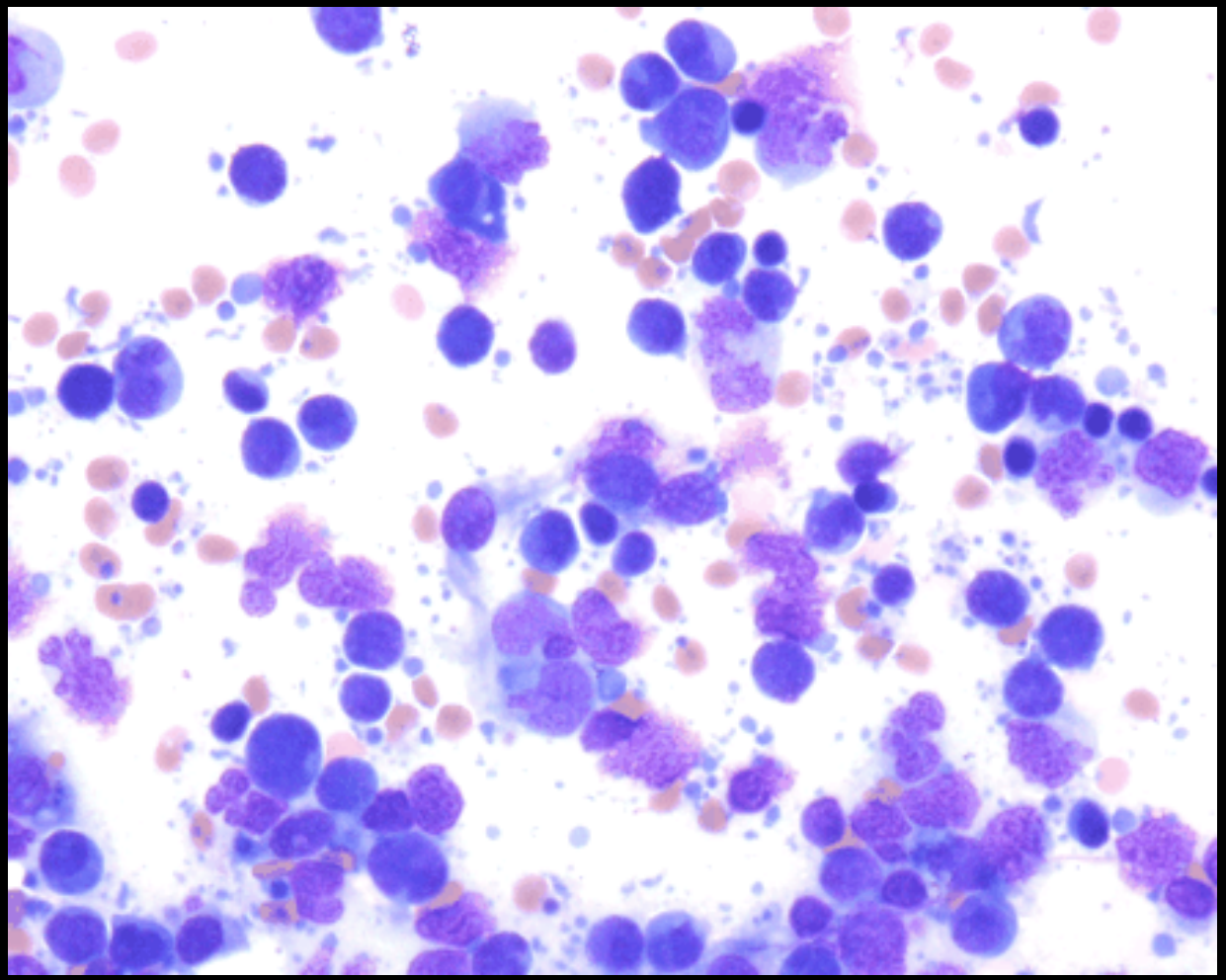
ALL



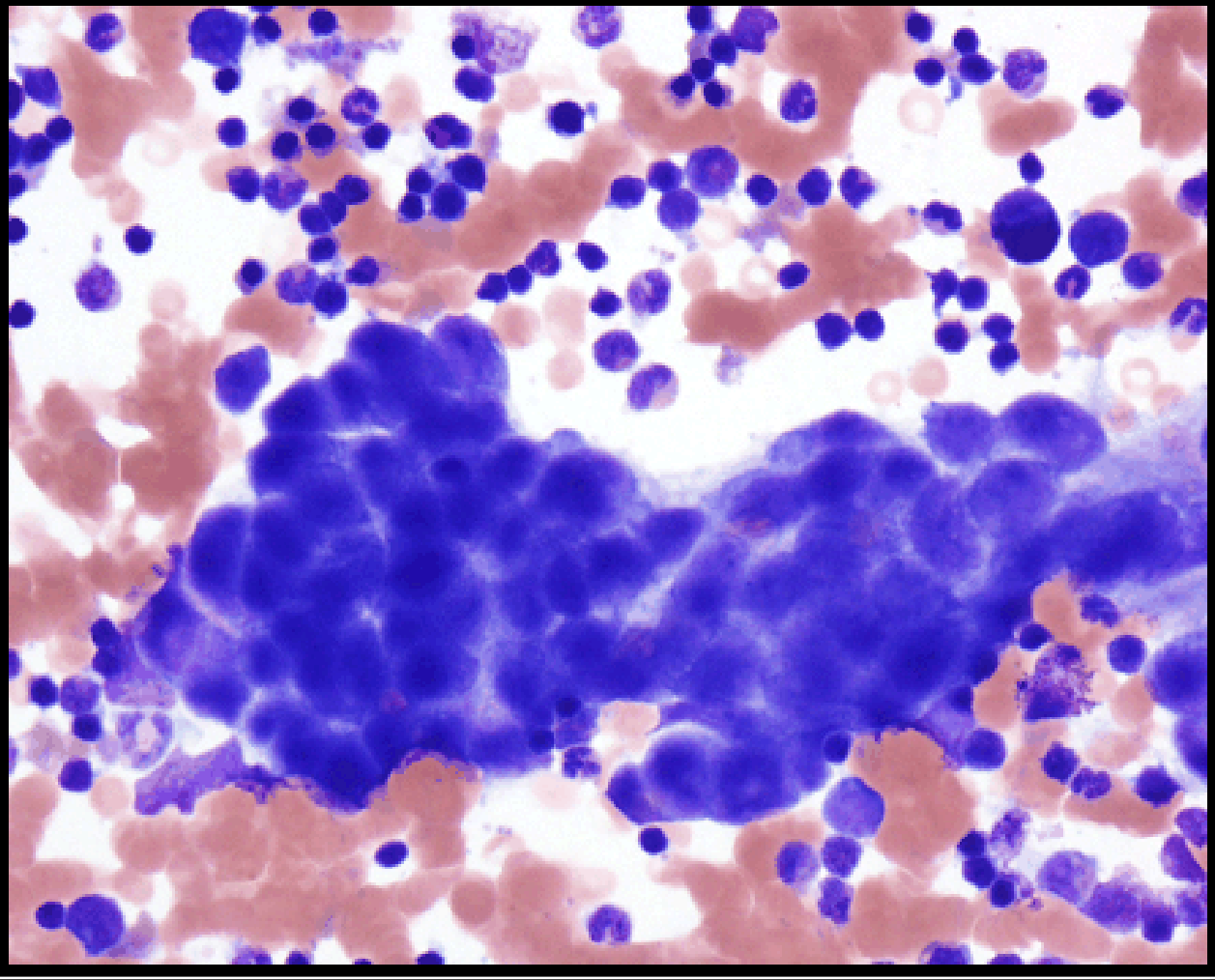
Multiple Myeloma



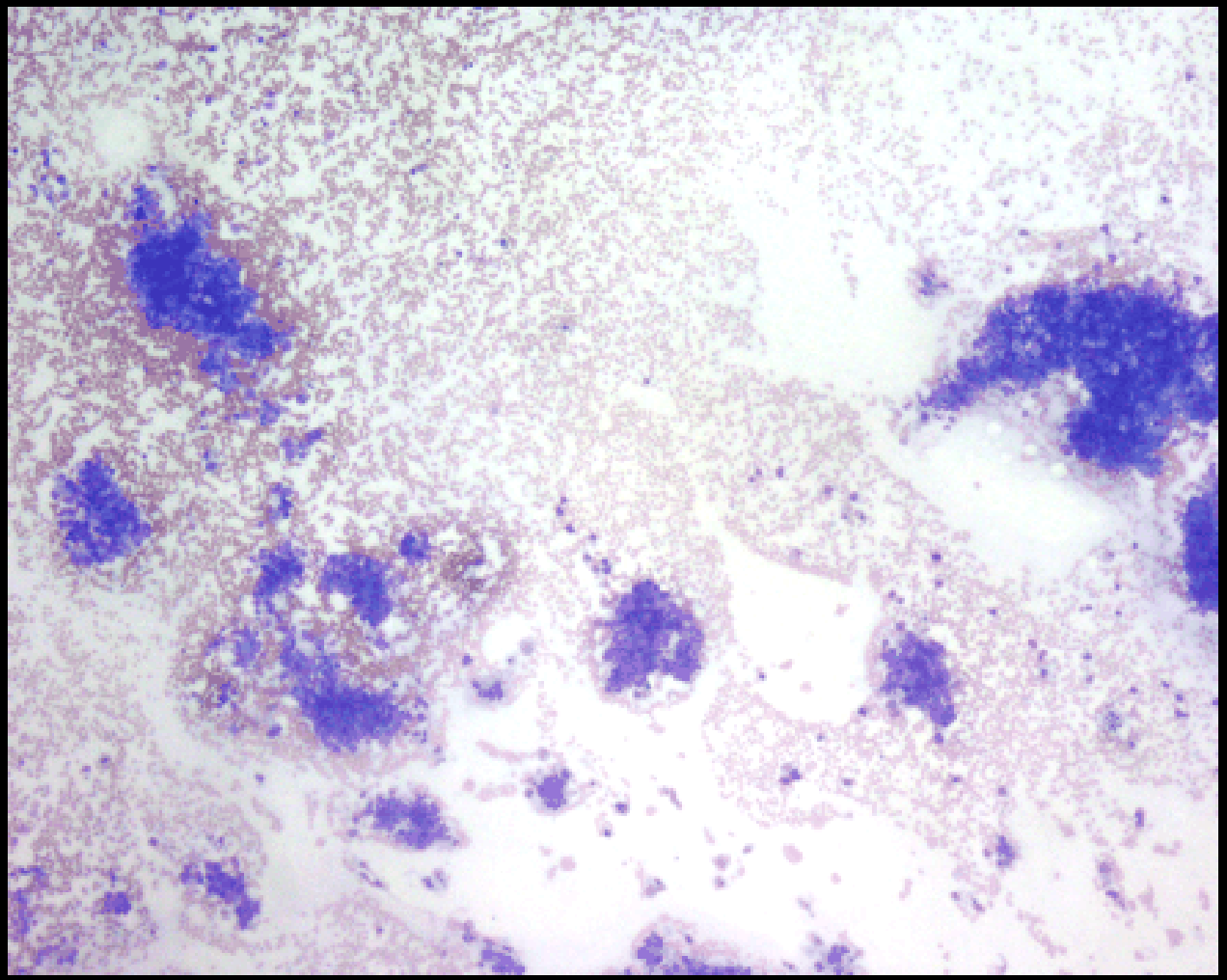
B-NHL Large Cell



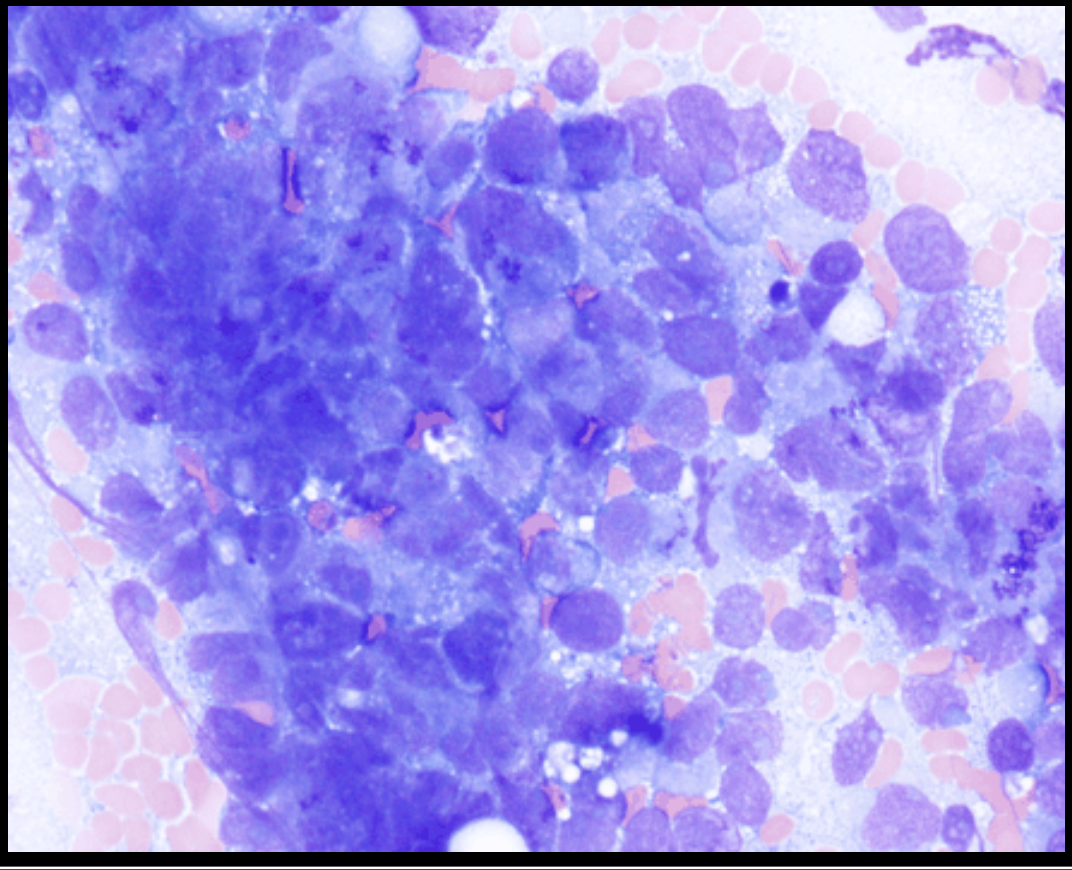
Neuroblastoma metastases



AdenoCR Prostate metastases

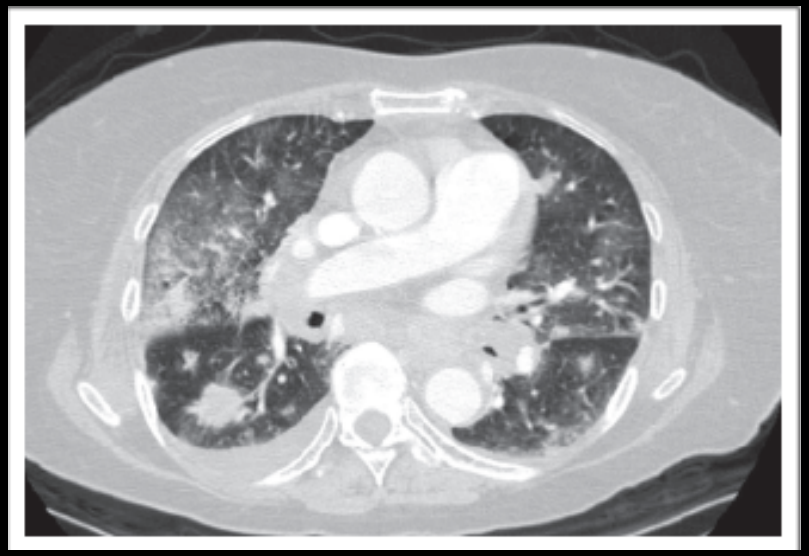


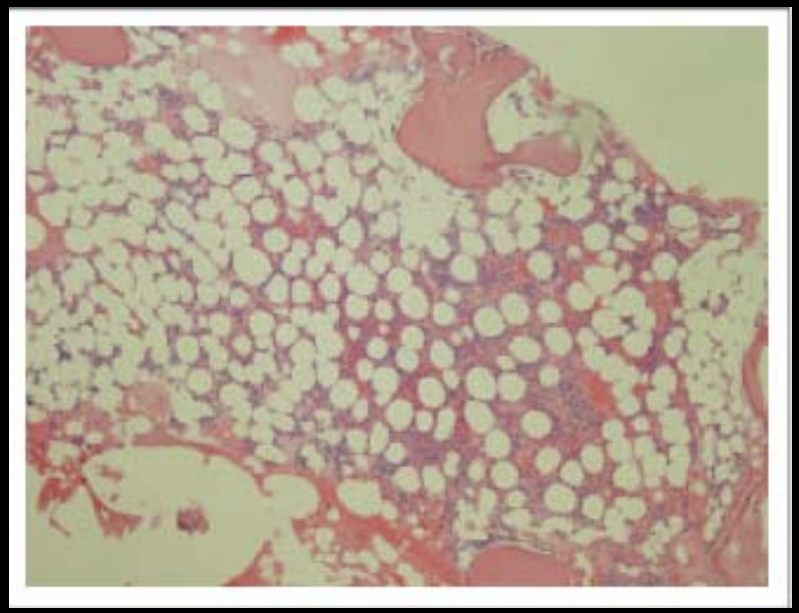
AdenoCR Prostate metastases



Paraneoplastic syndromes:
Severe Amegakaryocytic thrombocytopenia and lung cancer[1]

71 year woman, with fever, fatigue, cough;
WBC 11 x 10^9/L, Hb 11 g/dL, PLT 6 x 10^9/L





[1]Witteles WH et al. *JCO*, 2008

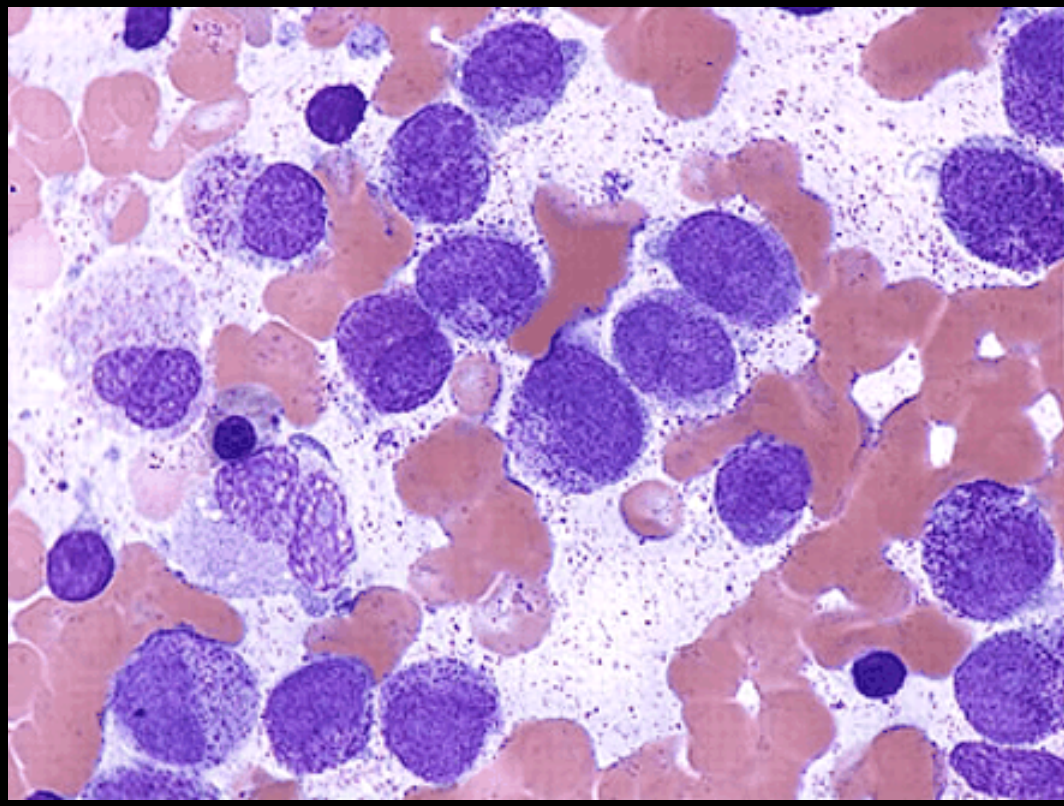
Thrombocytopenia and cancer: multiple origins

2. Accelerated platelet distruction

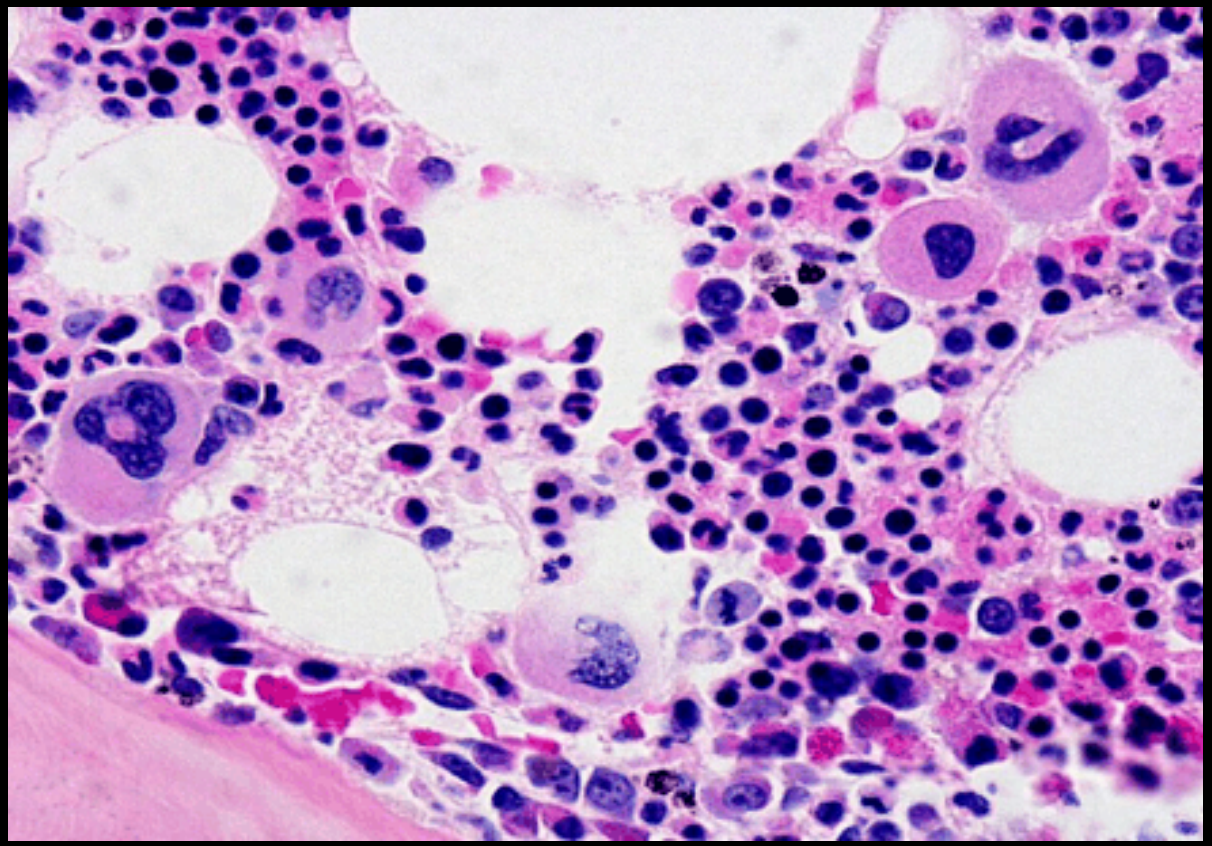
- Tumor-induced D.I.C.
  (APL, mucinous adenocarcinoma, pancreatic carcinoma)
- Tumor-induced TTP
- Immune mechanism
  (lymphoproliferative diseases)

APL

Female, 45 years old
Hemorrhagic diathesis
Hb 8 g/dL
WBC 0.9 x 10^9/L
PLT 23 x 109/L
PT 2.3 (INR)
aPTT 1.8 (Ratio)
Fibrinogen 65 mg/dL
D-Dimer test > 500 ng/mL



B-CLL and MKB hyperplasia



Immune Thrombocytopenia (IT) in B-CLL

Retrospective analysis in 1.278 patients

- 64 (5%) developed IT *during a median follow-up of 60 months from B-CLL diagnosis (14,2%, concomitantly)
- Probability of IT response higher for CTH ± steroids than i.v.Ig ± steroids (p=0.01)
- IT+ had poorer survival than IT- patients (p<0.001) independently from other prognostic variables

*= rapid and severe fall in platelet count; normal/augmented MKC in BM; no splenomegaly; no recent CHT (1 month)

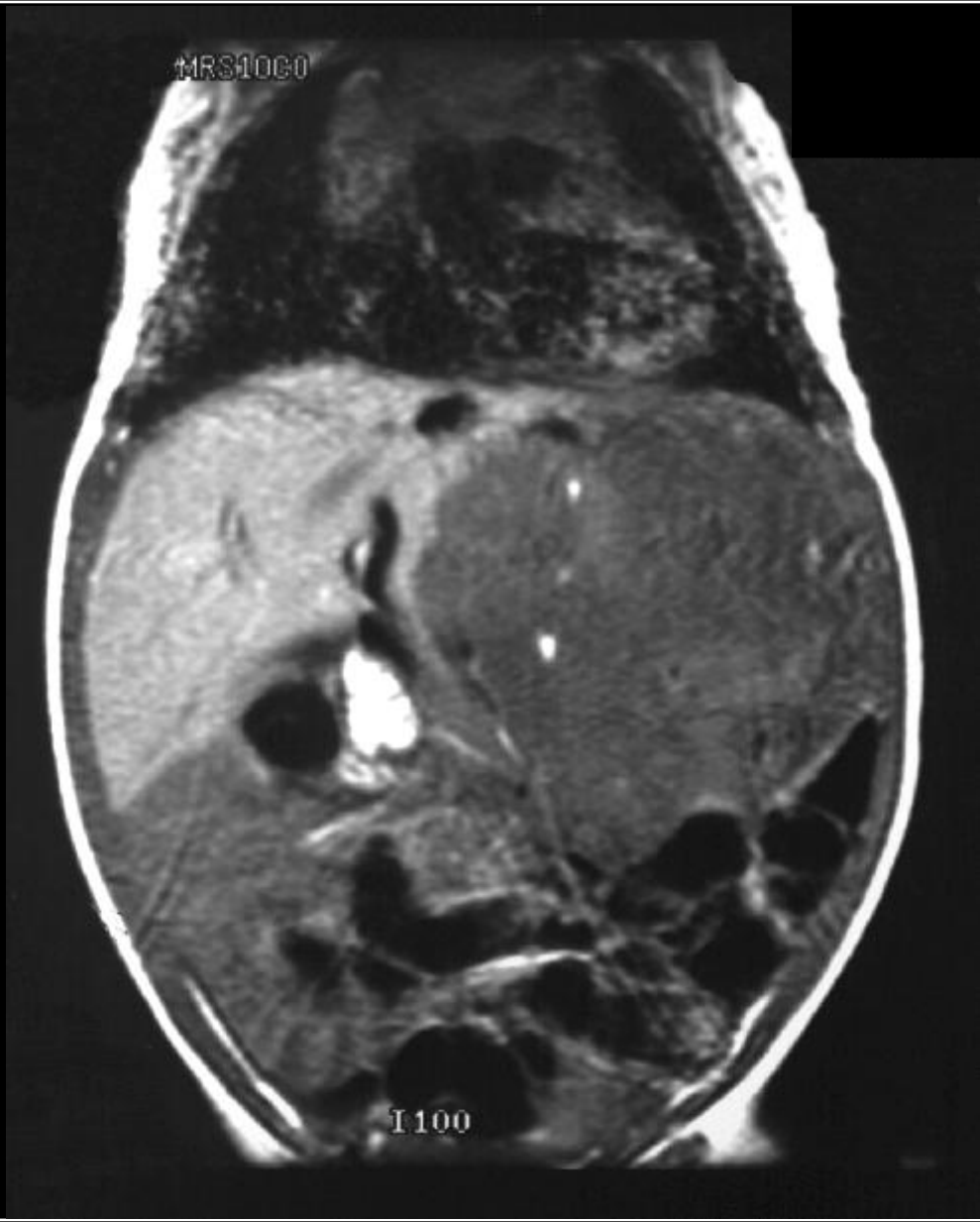
Visco C et al. Blood, 2008

Thrombocytopenia and cancer: multiple origins

3. Platelet sequestration

- Tumor-associated hypersplenism
- Hemangioendothelioma

Hemangioendothelioma

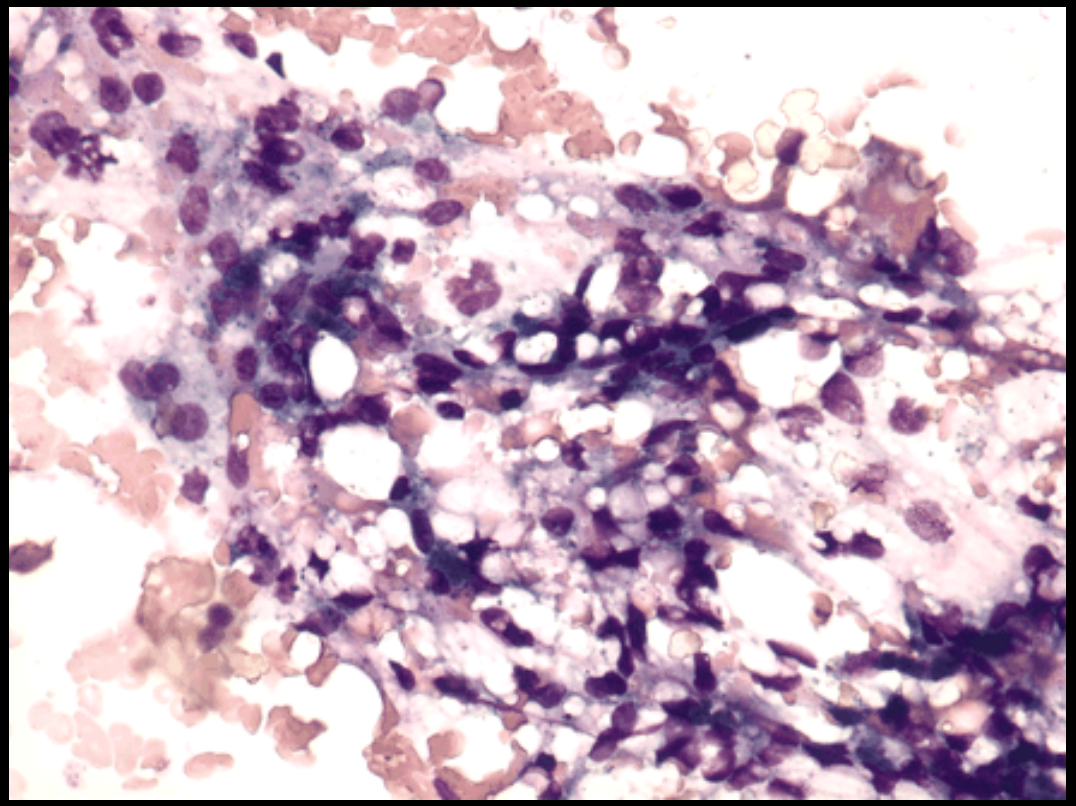


Thrombocytopenia and cancer: multiple origins

4. Reduced platelet production treatment-induced

- Chemotherapy
- Radiation treatment

Bone marrow after CHT

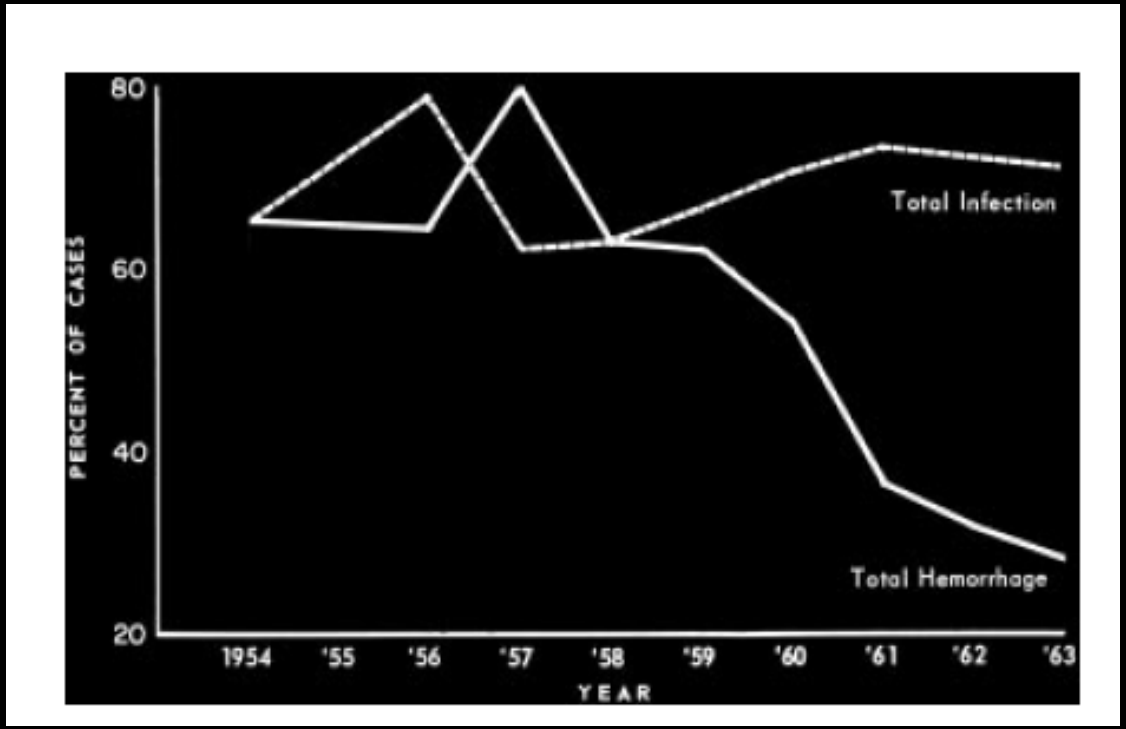


WHO Bleeding scale

- **Grade 0** no bleeding
- **Grade 1** petechial bleeding, no medical intervention
- **Grade 2** mild blood loss clinically significant, medical intervention, no transfusion
- **Grade 3** gross blood loss, medical intervention, requires transfusion
- **Grade 4** debilitating, life-threatening blood loss, retinal or cerebral associated with fatality

Rate of hemorrhagic deaths in AL patients not treated with PLT transfusion

Hersh et al; Causes of death in acute leukemia. A ten year study of 414 patients. *JAMA* 1965



Rate of bleeding in thrombocytopenic patients with AL (1)

Manual platelet counts !

ASA freely used as antipyretic drug and for pain !

Bleeding occurred on:

-38% of days	at PLT 10-20 x 10^9/L
-50% of days	at PLT 5-10 x 10^9/L
-65%-92% of days	at PLT < 5 x 10^9/L

Gaydos et al. *NEJM*, 1962

Rate of bleeding in thrombocytopenic patients with AL (2a)

Patients investigated: 102 AL (AML, ALL and 7 APL) and TCP post CTH, mean age 42 years

Design: prospective study on prophylactic platelet transfusion

End point: frequency and severity of hemorrhages

Period of observation: from 1983 to 1990

Gmur et al. *Lance*t 1991

Rate of bleeding in thrombocytopenic patients (2b)

Major bleeding (WHO 2-4)

31 episodes in 23 patients (20%); 3 hemorrhagic deaths

PLT count from 1 to 65 x 10^9/L

Gmur et al. *Lancet* 1991

Rate of bleeding in thrombocytopenic patients with AL (3)

Data from GIMEMA RCT (Rebulla et al, NEJM, 1997)

Patients investigated: 225 with AML (no APL) and TCP post CTH, age 16-74 years, male 52%

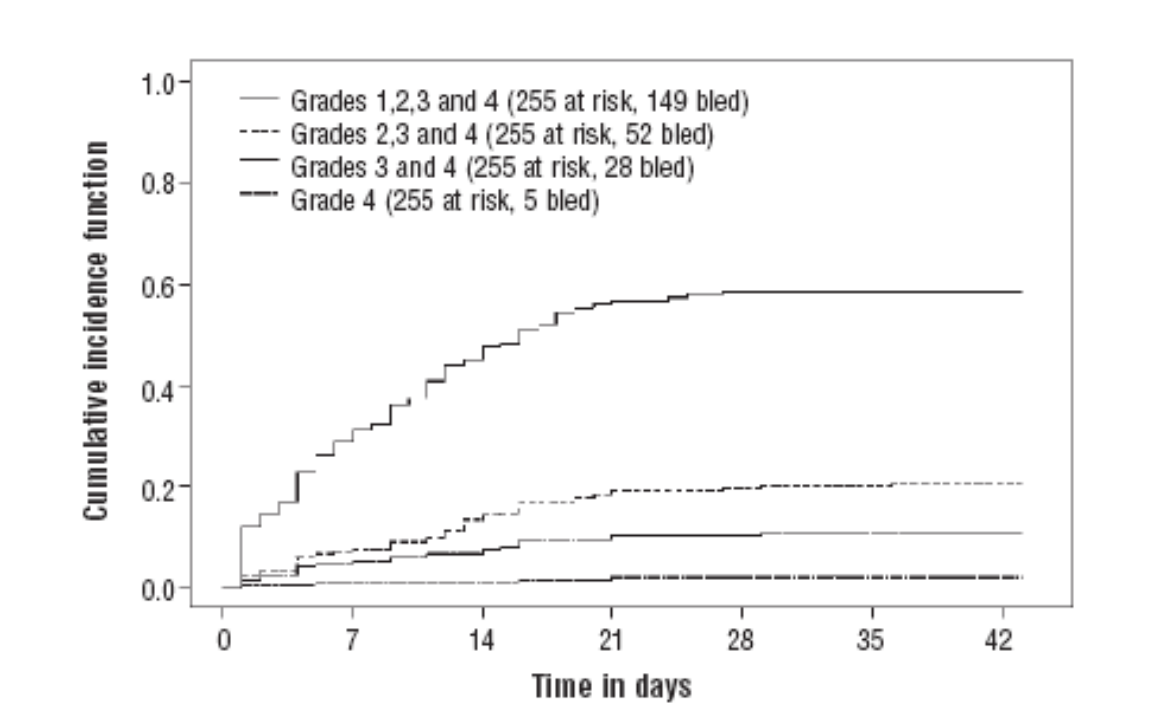
Design: 135 (52,9%) randomized to PLT transfusion at PLT count < 20 x 10^9/L (standard practice) compared with 120 (47,1%) at PLT count < 10 x 10^9/L (experimental arm)

End point: frequency and severity of hemorrhages

Period of observation: 7335 patient-days

Webert et al. *Haematologica*, 2006

Cumulative incidence for the occurrence of al least one bleeding of WHO grades 1-2, 2-4, 3-4 and 4



Patients with bleeding	n, %
Grade ≥ 1	149, 58%
Grade≥ 2	52, 20.4%
Garde≥ 3	28, 11%
Grade 4	5, 2%

Webert et al. *Haematologica*, 2006

Rate of thrombocytopenia **with need of PLT transfusion** in solid cancer patients

Retrospective analysis in 1.051 cancer patients (93, 9% with LNH)

Characteristics of cohort:

-age > 60 years: 396 (38%)

-high* risk CHT:105 (10%)

-n CHT course = 1: 766 (78%)

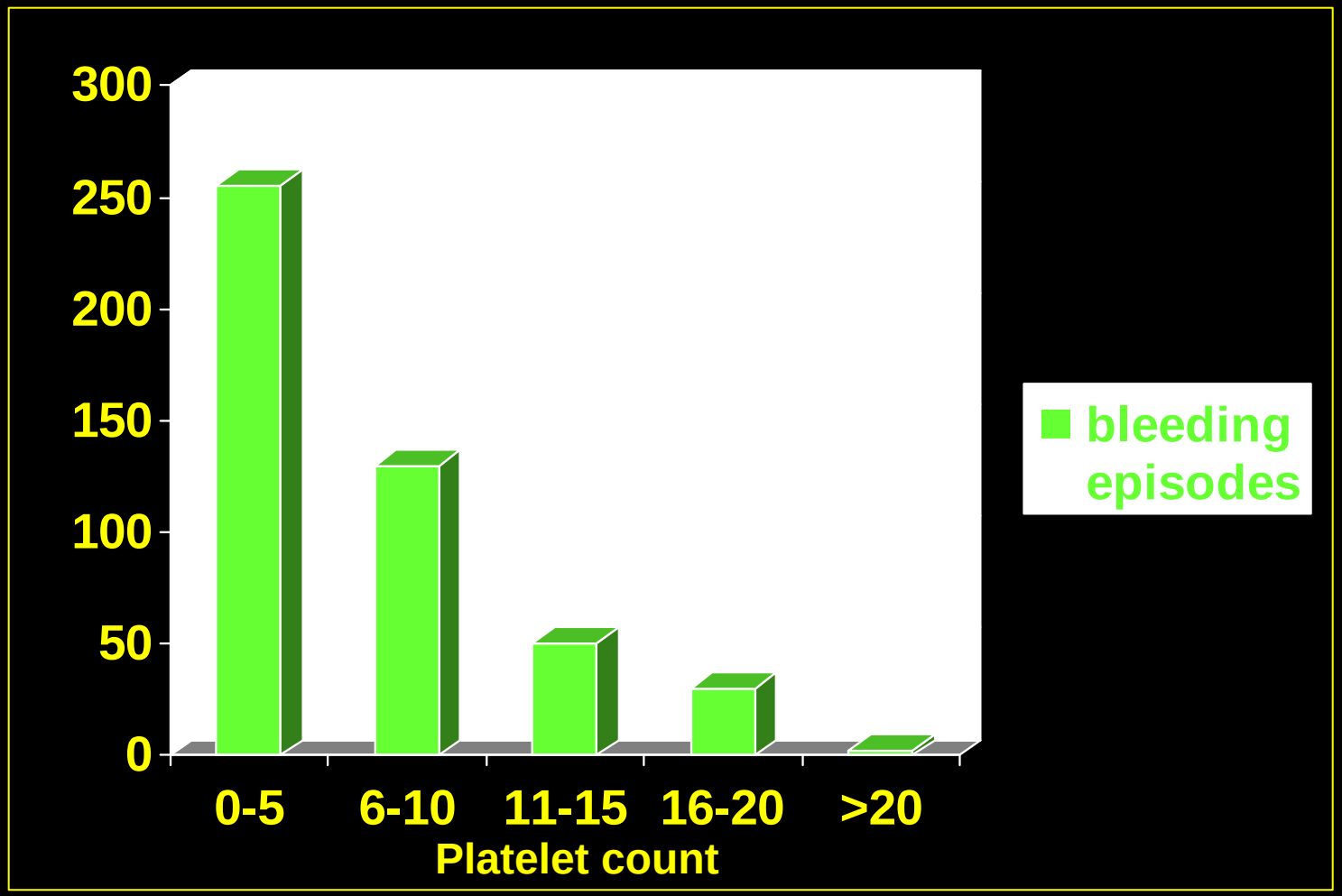
Results

-56 (5.3%) received PLT transfusion for severe TCP

*= doxorubicin > 90 mg^{m2}; epirubicin > 90 mg^{m2}, cisplatin > 100 g^{m2}; ifosfamide > 9 g^{m2}; cyclophosphamide > 1 $g^{m2;}$ etoposide > 500 mg^{m2}; cytarabine > 1 g^{m2}

Blay JY et al. *Blood,* 1998

Risk factors for bleeding in AL: blood platelet count ($x10^9$/L) per 1000 days at risk in AL patients



Gumr et al. *Lancet,* 1991

Risk factors for bleeding in AL

Variable	OR	CI	p
Mild bleeding (WHO 1-2)			
Antifungal medication	0.59	0.39-0.90	0.014
Clinical infection	1.98	1.00-3.92	0.05
Body temperature	1.52	1.25-1.85	<0.05
PLT transfusion	0.45	0.28-0.72	<0.05
PLT count	0.97	0.96-0.98	<0.05
Severe bleeding (WHO 3-4)			
PLT count	0.96	0.93-0.99	<0.05
Previous hemorrhage	2.55	1.18-5.49	0.0017

Webert et al. *Haematologica*, 2006

Factors associated with thrombocytopenia requiring PLT transfusion in cancer patients

Condition before CHT (multivariate analysis):

	OR	CI	p
PLT < 150 x 10^9/L	2.23	1.22-4.11	<0.001
Lymphocyte < 700/µL	3.37	1.77-6.44	<0.001
H.R. CTH	3.38	1.77-6.46	<0.001

Blay JY et al. *Blood*, 1998

Factors associated with risk of bleeding in cancer patients (1)

Retrospective analysis at John's Hopkins Oncology Center of 2.942 patients with cancer and thrombocytopenia (any etiology)

Condition	OR	CI	p
Uremia	1.64	1.33-1.79	<0.05
Hypoalbuminemia	1.32	1.22-1.43	<0.05
Previous hemorrhage	6.72	5.53-8.18	<0.05

* No correlation with PLT count

Friedman et al. *Transfusion* Med Rev, 2002

Factors associated with risk of bleeding in cancer patients (2)

Retrospective analysis at MD Anderson Cancer Center Center of 1.262 CHT and thrombocytopenia in 609 cancer patients

Major bleeding in 43 CHT (3%); total bleeding in 111 CHT (9%)

Condition	OR	CI	p
PLT < 75 x10^9/L	3.1	1.91-5.10	<0.001
Bone marrow meta	2.2	1.40-3.50	<0.01
Previous hemorrhage	5.4	2.90-10.2	<0.001
Cispaltin/carmustine	2.2	1.50-3.4	<0.002

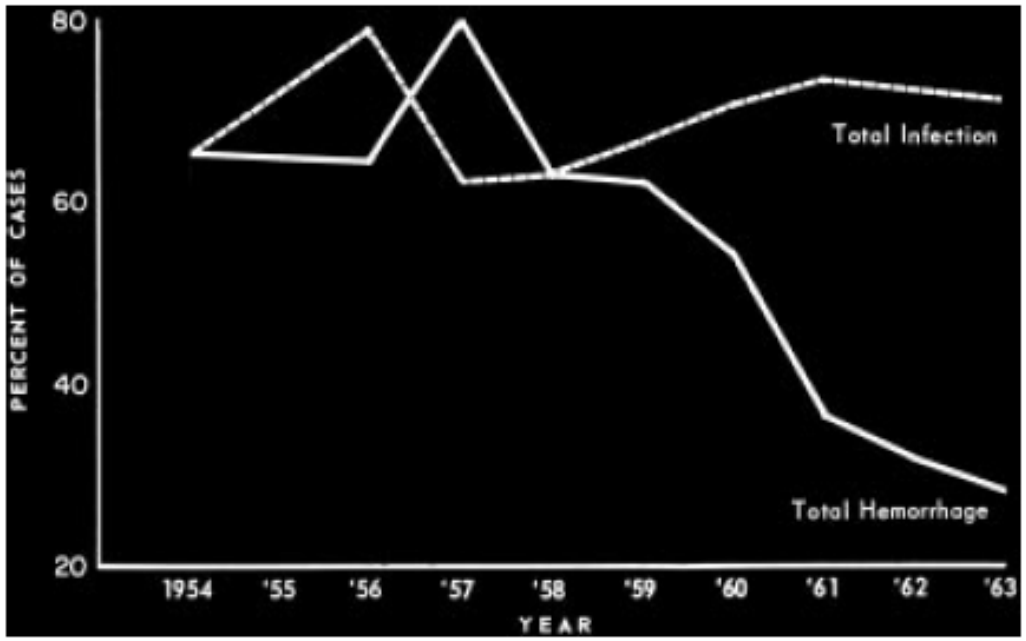
Elting et al. *J Clin Oncol*, 2001

PLT transfusions were shown to reduce mortality from hemorrhage in AL patients *

It is now an essential part of treatment of cancer and hematological malignancies

> 1.5 million components of platelets transfused each year in USA [1] and > 2.9 in Europe [2]

* Hersch et al. *Jama* 1965



[1]Sullivan MT et al. *Transfusion* 2005; [2] Maniatis A et al. *Blood transfusion in Europe, Elsevier*, 2005

Problems from increased use of PLT transfusion

- Increasing demand for PLT concentrate (recruitment of additional donors may not be sustainable)
- Transfusion-risk associated
- Platelet transfusion refractoriness

	CAUSE	PREVENTION
Infectious		
• AIDS	HIV-infected donor	Donor screening and testing Pathogen inactivation
• Hepatitis	Hepatitis B or hepatitis C virus infected donor	Donor screening and testing Pathogen inactivation
• CMV disease	CMV-infected donor	Donor testing Leucocyte reduction Pathogen inactivation
• Sepsis or septic shock	Contamination from the platelet donor's skin or from an occult or asymptomatic donor bacteraemia	Culture product 24 or more hours after collection Test for bacteria shortly before transfusion Pathogen inactivation
Immunological		
• Alloimmunisation	Leucocytes in platelets	Leucocyte reduction UVB irradiation
• Febrile reactions	HLA antibodies in transfusion recipient and IL-1β and IL-6 in platelets	Leucocyte reduction
• TRALI	Leucocyte antibodies, bioactive lipids, or CD40L in platelets	Exclude donors with leucocyte antibodies
• Anaphylaxis	Antibodies in patients reacting with IgA, haptoglobin, antibodies, or other plasma antigens	IgA-defi cient platelet donors Washed platelets
• GVHD	Engraftment of donor leucocytes in an immunosuppressed recipient	Gamma irradiation of platelets (25 Gy) Possibly pathogen inactivaton
• RhD alloimmunisation	Transfusion of platelets from RhD-positive donors to RhD-negative recipients	Administer Rh immune globulin within 48 h of transfusion
• Haemolysis	Anti-A and anti-B in donor's plasma	Exclude donors with high titres of anti-A or anti-B
• Hypotension	Generation of bradykinin by the bedside fi ltration of platelets in a patient taking angiotensinconverting enzyme (ACE) inhibitors	Pre-storage or in laboratory leucocyte reduction

Stroncek DF and Rebulla P. *Lancet,* 2007

Platelet transfusion: the “threshold” concept

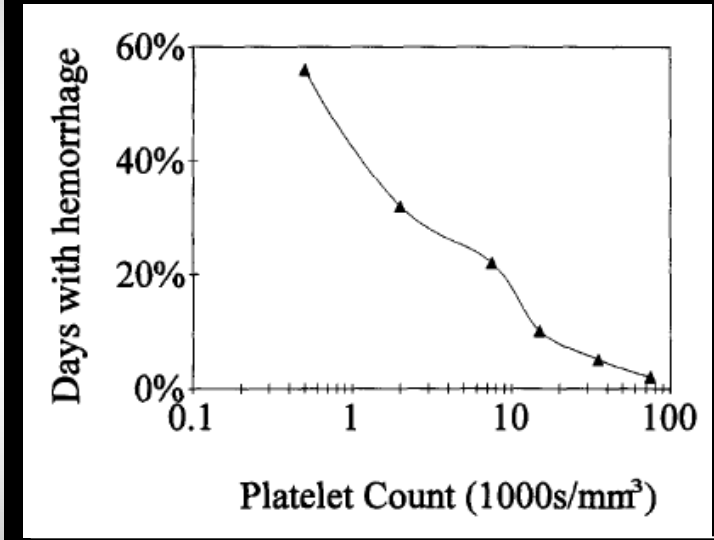
- Gaydos et al. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. *NEJM* 1962
- Freireich FJ. Effectiveness of platelet transfusion in leukemia and aplastic anemia. *Transfusion* 1966
- Higby DJ et al. The prophylactic treatment of thrombocytopenic leukemic patients with platelet: a double blind study. *Transfusion* 1974
- Murphy S et al. Randomized trial of prophylactic vs. therapeutic platelet transfusion in childhood acute leukemia. *Clin Res* 1974

Platelet transfusion: the $20x10^9$/L trigger

NIH consensus conference (*JAMA* 1987):

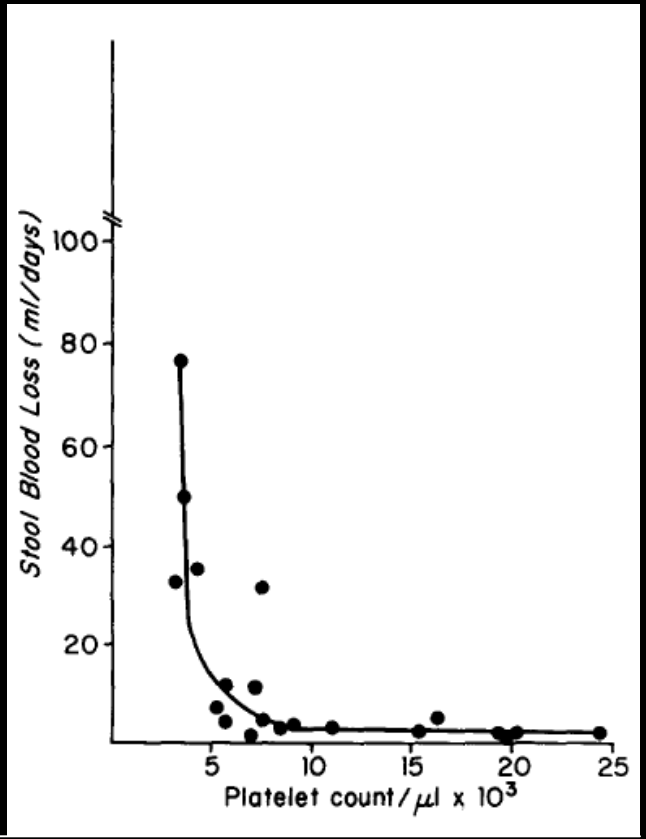
"*it is common practice to use preselected level of thrombocytopenia to decide when to transfuse platelets prophylactically. The value of 20 x 10^9/L is often used*"

Threshold ?



Gaydos et al. *NEJM*, 1962

"aspirinized" patients: no threshold value is seen



Slichter SJ et al. *Clin Hematol,* 1978

no "aspirinized patients: threshold value at 5 x 10^9/L

Beutler E. *Blood,* 1993

Searching a lower threshold

- Gmur J et al. *Lancet* 1991
- Gil-Fernandez JJ et al. *Bone Marrow Transplant* 1996
- Heckman KD et al. *J Clin Oncol* 1997
- Rebulla P et al. *NEJM* 1997
- Wandt H et al. *Blood* 1998
- Lawrence JB et al. *Leuk Lymphoma* 2001
- Zumberg et al. Biol *Blood Marrow Transplant* 2002

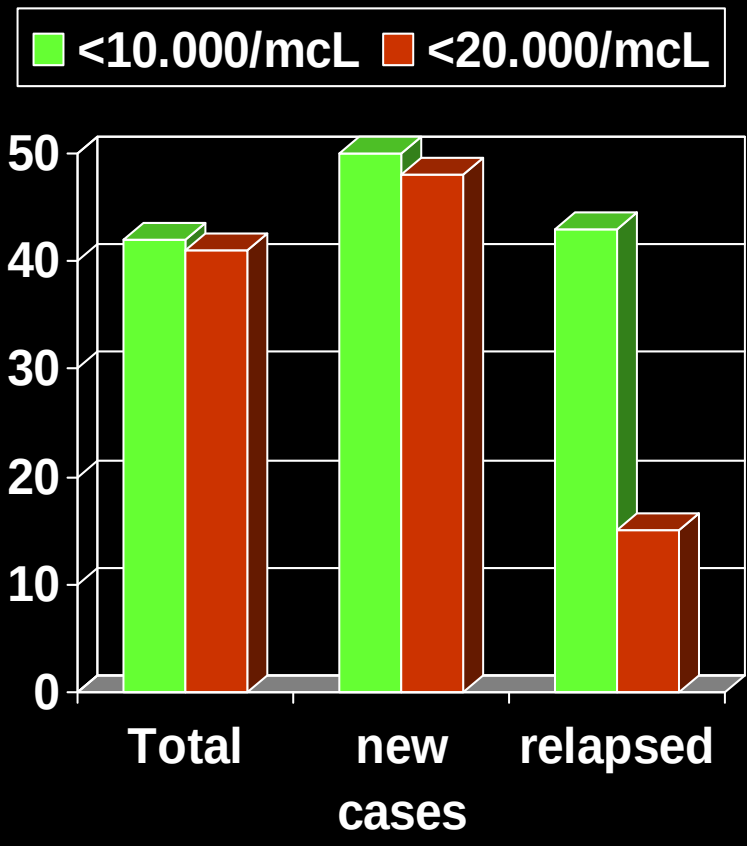
RCT

Rebulla et al. *NEJM,* 1997

TABLE 4. MAJOR END POINTS OF THE TRIAL.

END POINT	THRESHOLD, 10,000 PLATELETS/mm³ (N = 135)	THRESHOLD, 20,000 PLATELETS/mm³ (N = 120)
Patients with major bleeding episodes — no. (%)	29 (21.5)	24 (20.0)
1 episode	21 (15.6)	18 (15.0)
2 episodes	7 (5.2)	3 (2.5)
3 episodes	0	3 (2.5)
4 episodes	1 (0.7)	0
>4 episodes	0	0
Total days in hospital	4006	3330
Days with major bleeding episodes — no. (%)	123 (3.1)	65 (2.0)
Complete remission — no. of patients (%)	76 (56.3)	76 (63.3)
Death — no. of patients (%)	18 (13.3)	9 (7.5)
Infection	12	7
Cardiac failure	2	0
Acute renal failure	0	1
Trauma	1	0
Disseminated intravascular coagulation	1	0
Apoplectic stroke	0	1
Intestinal infarction	1	0
Cerebral hemorrhage	1	0

Heckman et al. *J Clin Oncol,* 1997



Bleeding episodes per patient

Platelet transfusion for patients with cancer: clinical practice guidelines "Threshold Guidelines"

- Consensus Conference on PLT transfusion, *Br J Haematol*, 1998
- ASCO guidelines, *J Clin Oncol*, 2001
- BCSH guidelines, *Br J Haematol*, 2003

PLATELET TRANSFUSION GUIDELINES

Condition	Guidelines	Level evidence	Grade
Acute leukemia	≤ $10x10^9$/L ≤ $20x10^9$/L, if: -fever -hemorrhage - hyper-WBC - coagulopathy	I	A
Hematopoietic cell transplantation	Similar to AL	III	B
Chronic, stable TCP (e.g.MDS, aplastic anemia)	No prophylactic PLT transfusion	IV	C
Solid tumor	≤ $10x10^9$/L ≤ $20x10^9$/L, if: -Bladder tumor -Necrotic tumors	IV	B

ASCO guidelines, *J Clin Oncol*, 2001

PLATELET TRANSFUSION GUIDELINES

Condition	Guidelines	Level evidence	Grade
Surgical/invasive procedure	40-50 x10^9/L in absence of coagulopathy	IV	C
Bone marrow aspiration/biopsy	Less than 20 x 10^9/L		
Lumbar puncture	Transfusion of <20 x 10^9/L		
Liver biopsy	< 20 x 10^9/L rate of bleeding similar to >150 x 10^9/L (3.4%)		
GI endoscopy	< 20 x 10^9/L no major complication (no biopsy)		
Broncoscopy + BAL	12% minor complication in < 50 x 10^9/L		
Transbronchial biopsy	Transfusion of <20 x 10^9/L		

ASCO guidelines, *J Clin Oncol*, 2001

Limitations of Guidelines

- Lack of blinding of clinicians in RCT:
  Detection bias and Performance bias
- Reduction of platelet use not achieved in all group in patients in RCT
- Low adherence to platelet trigger in clinical practice (protocol deviation in 38% and 15% of PLT transfusion in the 2 arms of Rebulla study)

in Netherlands only 50% of transfusion were strictly compliant with the stated threshold

(Eikenboom et al. *Transfusion Medicine*, 2005)

MDS and thrombocytopenia

- Heterogeneous hematopoietic disease associated with bone marrow failure (peripheral cytopenias) and a propensity for progression to AML[1]
- Two classification systems (FAB[2] and WHO[3])
- Several prognostic-scoring systems (IPSS[4] and WPSS[5])
- Standardized response criteria[6]

[1]Nimer SD. *Blood,* 2008; [2] Bennet JM et al. *Br J Haematol,* 1982; [3]Vardiman JW et al. *Blood,* 2002; [4]Greenberg P et al. *Blood,* 1997; [5]Malcovati L et al. *J Clin Oncol,* 2007; [6]Cheson BD et al. *Blood,* 2000; 2006

The incidence and impact of thrombocytopenia in MDS

M.D. Anderson Cancer Centre cohort[1]

2.410 MDS (1903 primary)

1.605 (67%) with thrombocytopenia (< 100 x 10^9/L) at referral

451 (17%) with severe thrombocytopenia (< 20 x 10^9/L) at referral

460/968 died without AML progression AND with a coded cause: 90 (20%) hemorrhage contributory cause and 48 (20%) the only cause

Bleeding reported in 50% at diagnosis in patients with PLT < 50 x 10^9/L[2] and from 3% to 18% during follow-up (moderate to severe hemorrhage[3-5])

[1]Kantarjian H et al. *Cancer,* 2007; [2]Wattel E et al. *Br J Haematol,* 1994; [3]Powel BL et al. *Leukemia*, 1988; [4]Rosenfeld CS et al. *Am J Clin Oncol*, 1997; [5]Picozzi VJ et al. *J Clin Oncol*, 1986

Prognostic scoring systems underweight the clinical importance of severe thrombocytopenia

	0	0.5	1.0	1.5	2.0
Blast %	< 5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3	-	-	-

IPSS

	0	1	2	3
WHO cat.	RA;RARS;5q-	RCMD; RCMD-RS	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
Transfusion*	No	Regular	-	-

WPSS

*= RBC transfusion dependency

IWG response criteria for hematologic improvement

Erythroid response

Platelet response (PLT pre-treatment< 100 x 10^9/L):

- Absolute increase of > 30 x 10^9/L (starting > 20 x 10^9/L)
- Increase from < 20 x 10^9/L to > 20 x 10^9/L

Neutrophil response

Cheson BD et al. *Blood,* 2000; 2006

Hematologic Improvement for PLT

Treatment	N patients	HI PLT% major/minor*
Lenalidomide	43	10/0
EPOr	40	0/0
Antithymocyte Ig	68	40/27
Cyclosporine A	50	16/12
Thalidomide	29	14/17
Arsenic trioxide	101	6/0
Valproic acid	18	11/0

*Cheson BD et al. *Blood,* 2000

Hypomethylating agents in MDS

Azacitidine and Decitabine have demonstrate anti-MDS activity[1]

FDA-approved for all type of MDS (FAB)[2,3]:

1. Significant reduction in risk of transformation to AML
2. Significant prolongation of survival in patients with high-risk MDS

[1]Santini V et al. *Ann Intern Med*, 2001; [2]Silverman LR et al. *J Clin Oncol,* 2002; [3]Kantarjian H et al. *Cancer,* 2006

Best response for MDS patients treated with azacitidine

	Pro. 8421		Pro. 8921		Pro.9221						8921+9221	
	AZA IV 48 pts		**AZA SC 70 pts**		**AZA SC 99 pts**		**Observation 41 pts**		**AZA SC 51 pts**		**AZA SC 169 pts**	
	N	%	N	%	N	%	N	%	N	%	N	%
CR	7	15	12	17	10	10	0	0	3	8	22	13
PR	1	2	0	0	1	1	0	0	2	4	1	1
HIEM	10	21	11	16	22	22	1	2	8	16	33	40
HIEm	2	4	3	4	8	8	4	10	4	8	11	17
HIPM	9	16	6	9	21	**21**	2	5	3	**6**	27	16
HIPm	0	0	2	3	3	3	0	0	1	2	5	3
HINM	2	4	0	0	8	8	1	2	2	4	8	5
HIMm	0	0	0	0	0	0	0	0	0	0	0	0
Overall	21	44	28	40	47	47	7	17	18	35	75	44

Response and outcome of MDS patients treated with decitabine

Results of RCT of 3 schedules of low dose decitabine[1]

95 patients with MDS high risk

33/68 (49%) patients with PLT pre-treatment < 100 x 10^9/L achieved a PLT response (> 100 x 10^9/L)

- 4/15 (27%) with PLT pre-treatment < 20 x 10^9/L
- 14/31 (45%) with PLT pre-treatment < 50 x 10^9/L
- 15/22 (68%) with PLT pre-treatment < 99 x 10^9/L

One-year survival by platelet count:

- 86% for responders vs 54 non-responders (p= 0.03)

[1]Kantarjian H et al. *Blood*, 2007

Thrombopoietic growth factors

-1994: purification and cloning human TPO

FIRST GENERATION

- Recombinant human thrombopoietins (rhTPO)
- PEG-rHuMGDF
- Recombinant TPO fusion proteins
- Promegapoietin (TPO/IL3 fusion protein)

-rhTPO and PEG-rhMGDF studied in several thrombocytopenic disorders

-1998: clinical trials stopped for auto Ab against PEG-rhMGDF and endogenous TPO in some patients→ no development of rhTPO

Thrombopoietic Growth Factors

Second generation: same effects on rTPO, without antigenicity property (no homology sequence with TPO)

- TPO peptide mimetics
  - Fab 59
  - AMG 531 (s.c. administration)
  - Peg TPOmp
- TPO non-peptide mimetics
  - Eltrombopag (orally available)
  - AKR-501 (orally available)
- TPO agonist antibodies
  - Minibodies (VB22B sc(FV)2)
  - MA01G4G344

Kuter DJ. *Blood* 2007

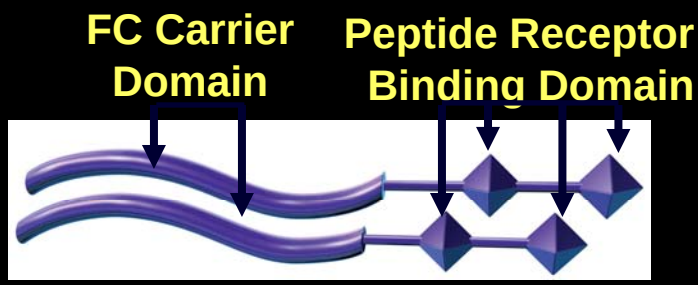
Thrombopoietic agents currently in clinical development

Agents	*Clinical development*
Peptides	
• Romiplostim	Currently approved for ITP. Current clinical trials for myelodysplasia and chemotherapy induced thrombocytopenia
• Fab59	No human studies reported
• PEG-TPOmp	No human studies reported
Non-peptide small molecules	
• Eltrombopag	Currently approved for ITP.
•	Current clinical trials for chemotherapy-induced thrombocytopenia and HCV – induced TCP
• AKR-501	Current clinical trials for ITP, liver disease and chemotherapy-induced thrombocytopenia
• LGD-4665	Studies in normal subjects reported
• Butyzamide	No human studies reported
Monoclonal antibodies	
• VB22B sc (Fv)2	No human studies reported
• MA01G4G344	No human studies reported

George JN et al. *Haematologica,* 2008

AMG531: Recombinant Protein

- "Peptibody"
  - consists of a carrier Fc domain linked to multiple Mpl-binding domains[1]
- MW = 60,000
- No sequence homology with TPO
- Binds to and activates receptor Mpl (TPOr); stimulates megakaryocyte growth, maturation[1, 2]

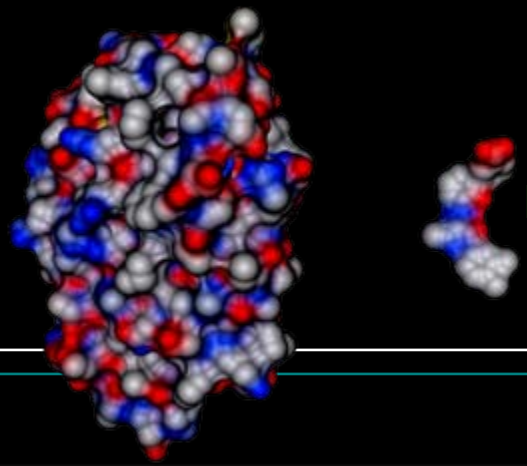


[1]Broudy VC and Lin NL. *Cytokine*, 2004; [2]Wang B et al. *Clin Pharmacol Ther*, 2004

Eltrombopag: Platelet Growth Factor

- Oral TPOr agonist: stimulates megakaryocyte proliferation and differentiation
- Small molecule; MW = 442
- Does not prime platelets for activation and aggregation[1]
- Less immunogenic potential than peptidyl agents
- Clinical studies in ITP, liver disease and CIT

Thrombopoietin (TPO)
MW 64,000



Eltrombopag (TPOr-agonist)
MW 442

Reference	Study	Number patients	Efficacy	Rate Respo. N(%)
NEJM AMG531	Open label Placebo-contr	12 4 (P) 17 (D)	Plt > 50	7(58) 1(25) 13(76)
BJH AMG531	Open label	15	Plt > 50	9(60)
NEJM Eltrombopag	Placebo-contr	27 (P) 27(D 50mg) 26 (D75mg)	Plt > 50	3(11) 19(70) 21(81)
Lancet AMG531	Placebo-contr	21sp(P) 41sp(D) 21 ns(P) 41ns(D)	Plt > 50	0(0) 16(38) 1(2) 25(56)
Total		73(P) 180(D)		5(7) 110(61)

Reference	Study	Number patients	Serious SE
NEJM AMG531	Open label Placebo-contr	24(D) 4 (P) 17 (D)	3 2 1
BJH AMG531	Open label	16	1
NEJM Eltrombopag	Placebo-contr	29 (P) 30(D 30mg) 30 (D75mg) 28(D75mg)	4 2 4 3
Lancet AMG531	Placebo-contr	41(P) 83(D)	5 (2†) 6 (1†)
Total		74(P) 212(D)	11(14.8%) 20(9.4%)

Potential risks of thrombopoietic agents

Adverse event	*Clinical evidence*
• *Rebound* thrombocytopenia	Severe thrombocytopenia (platelet counts < baseline level), when thrombopoietic agents are stopped.
• Thrombosis	No evidence for an increased risk from current clinical trials; risk could be revealed with long-term use.
• Increased marrow reticulin	In a clinical trial of rhTPO in patients with AML, 8 of 9 patients had reversible increased marrow reticulin. Increased, reversible marrow reticulin has been reported in ITP patients in romiplostim clinical trials.
• Acceleration of hematologic malignancies	In a phase 1/2 clinical trial of romiplostim, 6 of 44 patients with MDS had increased myeloblasts and 1 patient progressed to LAM

George JN et al. Haematologica, 2008

Dose Evaluation Study Of Oral Eltrombopag In Patients With Sarcoma Receiving The Adriamycin And Ifosfamide Regimen

This study is currently recruiting participants.
Verified by GlaxoSmithKline, October 2008

Sponsored by: GlaxoSmithKline
Information provided by: GlaxoSmithKline
ClinicalTrials.gov Identifier: NCT00358540

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

1. **Recruiting** Study of AMG 531 to Evaluate the Safety & Efficacy in Patients With Non-Hodgkin's Lymphoma
   Condition:LymphomaInterventions:Drug: AMG 531; Drug: Rituximab; Drug: Cyclophosphamide; Drug: Vincristine; Drug: Doxorubicin; Drug: Dexamethasone; Drug: Methotrexate; Drug: Cytarabine; Drug: Placebo
2. **Recruiting** AMG 531 in Patients With Advanced Malignancy Receiving Treatment With Carboplatin
   Condition:Solid Tumors Interventions:Drug: AMG 531; Drug: Carboplatin; Drug: Adriamycin; Drug: Ifosfamide
3. **Recruiting** Dose/ Schedule Finding Trial of AMG 531 for Chemotherapy-Induced Thrombocytopenia (CIT) in Non-Small Cell Lung Cancer (NSCLC)
   Conditions:Lung Cancer; Chemotherapy-Induced Thrombocytopenia; Non-Small Cell Lung Cancer; Cancer; Lung Neoplasms; Oncology; Solid Tumors; Thrombocytopenia Interventions:Biological: AMG 531; Drug: Placebo
4. **Recruiting** A Safety and Efficacy Study to Evaluate AMG 531 Treatment in Subject With Myelodysplastic Syndrome Receiving Revlimid
   Conditions:Myelodysplastic Syndromes; Thrombocytopenia Interventions:Biological: AMG 531; Drug: Placebo
5. **Recruiting** Determination of Safe and Effective Dose of AMG 531 in Subjects With MDS Receiving Hypomethylating Agents
   Conditions:MDS; Myelodysplastic Syndromes; Thrombocytopenia Interventions:Drug: Placebo; Biological: AMG 531
6. **Completed** A Dose and Schedule Finding Trial With AMG 531 for CIT in Adults With Lymphoma
   Conditions:Chemotherapy-Induced Thrombocytopenia; Hodgkin's Lymphoma; Non-Hodgkin's Lymphoma; Cancer; Oncology; Thrombocytopenia Intervention:Biological: AMG 531
7. **Recruiting** Evaluating the Safety of Long Term Dosing of Romiplostim (Formerly AMG 531) in Thrombocytopenic Subjects With Myelodysplastic Syndromes (MDS)
   Conditions:Hematology; MDS; Myelodysplastic Syndromes; Thrombocytopenia Intervention:Drug: Romiplostim (formerly AMG 531)
8. **Completed** Determination of Safe Dose of Romiplostim (Formerly AMG 531) in Subjects WithMDS
   Conditions:MDS; Myelodysplastic Syndromes; Refractory Cytopenias; ThrombocytopeniaInterventions:Drug: Romiplostim; Drug: Romiplostim; Drug: Romiplostim; Drug: Romiplostim; Drug: Romiplostim
9. **Recruiting** Romiplostim Treatment of Thrombocytopenia in Subjects With Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)
   Conditions:MDS; Myelodysplastic Syndromes; Thrombocytopenia Interventions:Biological: Romiplostim; Drug: Placebo

Evaluating safety and efficacy of AMG 531 for the treatment of thrombocytopenic patients with myelodysplastic syndrome (MDS): Preliminary results of a phase 1/2 study.

- 28 MDS patients, PLT baseline count < 5 x 10^9/L, treated weekly with romiplostim
- 17 (61%) achieved a platelet response (median platelet count 25 x 10^9/L; median peak platelet count 130 x 10^9/L)
- 11/18 treated for at least 12 ws. achieved a durable response (at least 8 consecutive ws.)
- No treatment-related severe AEs occurred

Kantarjian H et al. *ASCO Meeting,* 2007

Management of bleeding with "hemostatic" drugs[1]

In cancer thrombocytopenic patients:

- DDAVP[2,3]
- Conjugate estrogen[3]
- rFVIIa[4-9]
- Vitamin k[3]
- Tranexamic acid[3]

[1]Mannucci PM and Levi M. *NEJM*, 2007; [2]Castaman G et al. *Haematologica*, 1997; [3]Chiu J et al. *Curr Opin Hematol*, 2002; [4]Robert H et al. *Blood,* 2004; [5]Goodnought LT. *Semin Hematol*, 2004; [6]Vidarsson B et al. *Thromb Haemostas*, 2000; [7]de Fabritiis P et al. *Haematologica,* 2004; [8]Pihusch M et al. *J Thromb Haemostas,* 2005; [9]Marietta M et al. *J Thromb Haemostas,* 2006

- Current guidelines of American Heart Association recommend ASA therapy in all cases of Acute Coronary Sndromes[1]
- Guidelines developed for patients with normal platelet count
- Patients with cancer exclude from RCT of anti-thrombotic therapy

but

- 15% cancer patients develop thrombosis[2]
- 10% cancer patients have thrombocytopenia

Impact of ASA therapy in cancer patients with thrombocytopenia and Acute Coronary Syndrome (ACS)[3]

[1]Braunwald E et al. *J Am Coll Cardiol*, 2002; [2]Lip Gy et al. *Lancet Oncol,* 2002; [3]Sarkiss MG et al. *Cancer,* 2007

Retrospective analysis at M.D. Anderson CC (year 2001)

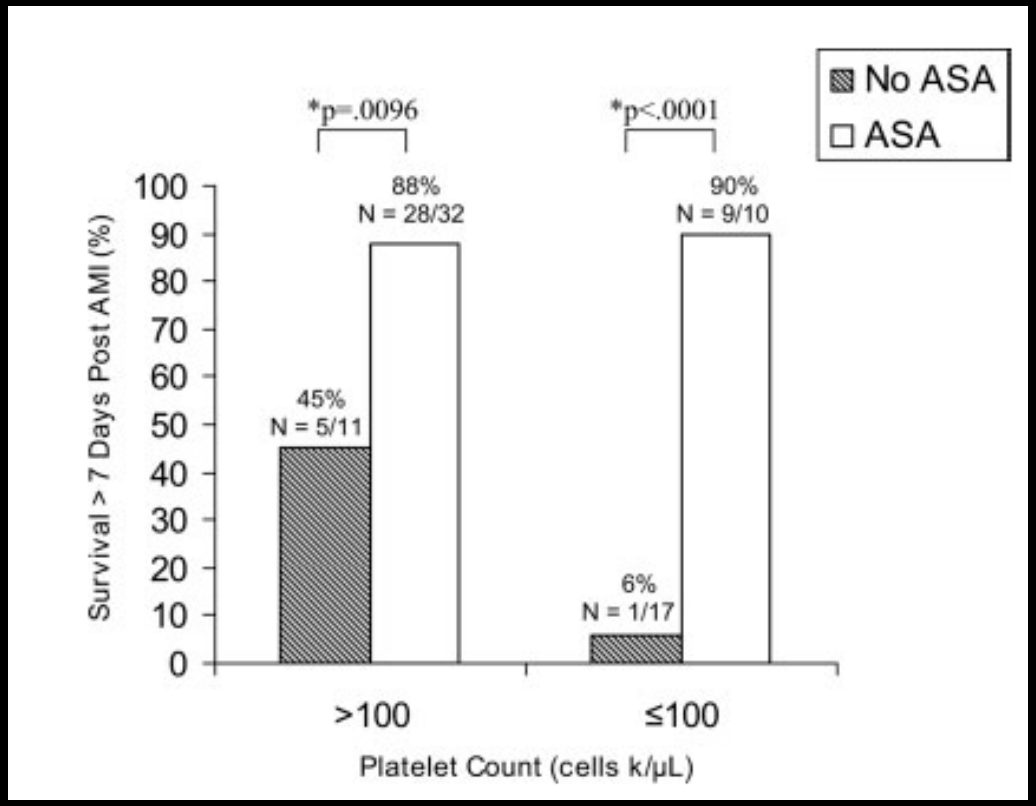
Demographics of Cancer Patients With Acute Myocardial Infarction

Characteristics	Total N = 70 No. (%)	>100 k/μL N = 43 No. (%)	≤100 k/μL N = 27 No. (%)	*P
Women	23 (33)	15 (35)	8 (30)	
Men	47 (67)	28 (65)	19 (70)	
Age, mean ± SD	67 (10)	68 (10)	64 (9)	
Hypertension	39 (57)	25 (61)	14 (52)	
Diabetes mellitus	18 (26)	11 (27)	7 (26)	
Hyperlipidemia	38 (54)	23 (53)	15 (56)	
Smoking	46 (66)	28 (65)	18 (67)	
Family history	22 (31)	15 (35)	7 (26)	
Coronary artery disease	20 (29)	13 (32)	7 (26)	
Cancer diagnosis				
Solid	54 (77)	40 (93)	14 (52)	.0001
Hematologic	16 (23)	3 (7)	13 (48)	

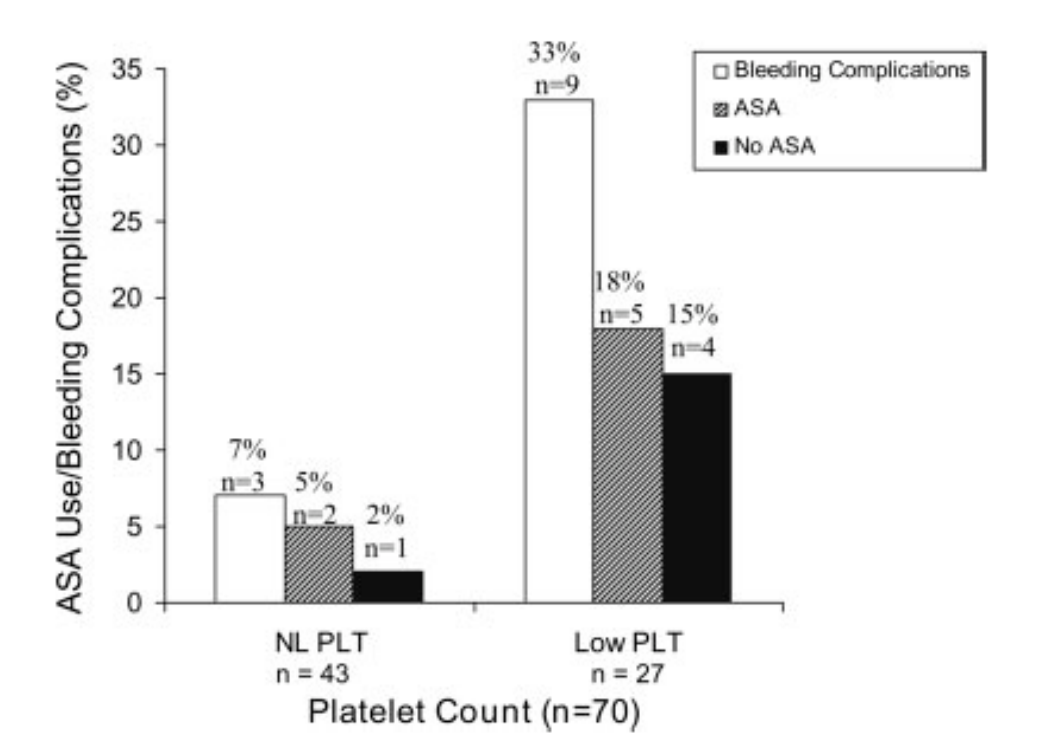
Clinical Parameters of Cancer Patients Presenting With Acute Myocardial Infarction

Characteristics	Total N = 70 No. (%)	>100 k/μL N = 43 No. (%)	≤100 k/μL N = 27 No. (%)	P
Heart rate, beats/min on admission		92 (60, 180)	112 (68, 150)	.02*
Systolic blood pressure, mmHg		118 (70, 187)	115 (60, 160)	
Hemoglobin, gm/dL	10 (6, 16)	11 (6, 16)	9 (6, 13)	.0002†
Platelet count, cells k/μL	169 (4, 498)	225 (121, 498)	32 (4, 100)	<.0001*
ST segment elevation	17 (24)	9 (21)	8 (30)	
Troponin I, ng/mL	4 (0, 77)	3 (0, 48)	5 (2, 77)	
CK-MB, ng/mL	12 (1, 253)	10 (1, 253)	18 (2, 110)	
% Left ventricular ejection fraction	50 (20, 70)	48 (20, 70)	55 (23, 68)	

Retrospective analysis at MD Anderson CC (year 2001)



Retrospective analysis at MD Anderson CC (year 2001)



No major gastrointestinal bleeding, intracranial hemorrhage of fatal bleed occurred