9° International Conference on
Thrombosis and Hemostais Issues in Cancer
Bergamo 13 – 15 April, 2018

Management of thrombocytopenia in Cancer

Giancarlo Castaman

Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy

Disclosures for Giancarlo Castaman

In compliance with CME policies, 9th ICTHIC requires the following disclosures, related to the speaker's presentation, to the session audience :

Research Support/P.I.	*No relevant conflicts of interest to declare*
Employee	*No relevant conflicts of interest to declare*
Consultant	*No relevant conflicts of interest to declare*
Stockholder	*No relevant conflicts of interest to declare*
Advisory Board	*No relevant conflicts of interest to declare*
Speakers Bureau	*No relevant conflicts of interest to declare*
Other (Specify)	*No relevant conflicts of interest to declare*

Summary

- Pathogenesis, epidemiology and risk factors
- Platelets: the source material
- Assessment of quality of treatment
- Refractoriness
- Risks with platelet transfusion
- Antithrombotic treatment in cancer patients with thrombocytopenia

PATHOGENESIS OF THROMBOCYTOPENIA IN PATIENTS WITH SOLID TUMORS

- Myelotoxic chemotherapy regimens
- Disseminated intravascular coagulation (DIC)
- Bone-marrow involvement by tumor cells
- Drugs (e.g., heparin)

PATHOGENESIS OF THROMBOCYTOPENIA IN PATIENTS WITH BLOOD MALIGNANCIES

- Bone-marrow infiltration
- Myelotoxic chemotherapy regimens
- Disseminated intravascular coagulation (DIC)
- Splenomegaly
- Immune thrombocytopenia (e.g. during chronic lymphocytic leukemia)

GRADES OF THROMBOCYTOPENIA

	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Platelet count	<LLN – 75,000/µL	<75,000 – 50,000/µL	<50,000 – 25,000/µL	<25,000/µL	Death

CHEMOTHERAPY-RELATED THROMBOCYTOPENIA

	PERCENTAGE OF GRADE 3-4 THROMBOCYTOPENIA
Cisplatin monotherapy	4%
Gemcitabine monotherapy	3.7%
Cisplatin + Gemcitabine	37%
Ifosfamide + doxorubicin + dacarbazine	79%
Ibritumomab tiuxetan conjugated with Yttrium-90	~ 100%
bortezomib	31%

Kuter DJ. Oncology 2015; 29: 282-294; Ten Berg MJ, et al. Drug Saf 2011; 34: 1151-1180; Wu Y, et al. Clin Ther 2009; 31 (Pt2):2416-2432.

ICTHIC

Mean Fibrinogen and Platelet count in Acute Leukemia of different types at diagnosis

AL Type	Fibrinogen (mg/dL)	Platelet Count (x $10^3/\mu L$)
AML (n = 91)	301 ± 104	79 ± 78
ALL (n = 49)	316 ± 113	78 ± 79
APL (n = 62)	***144 ± 78****	***35 ± 25****

* P < 0.001 vs ALL and AML

Rodeghiero & Castaman, 1988

Risk factors for bleeding in APL*

- Low Platelet Count
- Low Fibrinogen
- Prolonged PT
- High blast cell count, older age
- Decrease of α_2-antiplasmin

* Compiled from historical studies up to 1989

blood 1990 75: 2112-2117

Early deaths and anti-hemorrhagic treatments in acute promyelocytic leukemia. A GIMEMA retrospective study in 268 consecutive patients [see comments]

F Rodeghiero, G Avvisati, G Castaman, T Barbui and F Mandelli

Table 1. Patient Outcome by Anti-Hemorrhagic Treatment

	Heparin N = 94 (35.1%) (%)	Supportive Treatment N = 107 (39.9%) (%)	Anti-Fibrinolytic N = 67 (25%) (%)
CR	58 (61.7)	66 (61.7)	43 (64.2)
Failure	13 (13.8)	14 (13.1)	6 (8.9)
Early hemorrhagic deaths	9 (9.6)	11 (10.3)	5 (7.5)
Early death from other causes	3 (3.2)	4 (3.7)	2 (3.0)
Late deaths	11 (11.7)	12 (11.2)	11 (16.4)

Table 5. Supportive Treatment During Induction Therapy in the Different Treatment Groups

Patients	Units of Platelet Concentrates Mean (SD)	Units of Packed RBCs Mean (SD)
Heparin*	61.9 (41.9)	5.5 (2.8)
Supportive treatment	49.6 (36.5)	5.7 (3.5)
Anti-fibrinolytic	44.5 (30.7)	4.5 (2.5)

*The platelet concentrate consumption was significantly greater in the heparin-treated group than other groups ($P < .01$).

WBC > 10.000/μL and low platelet count highly predictive of death < 24 hours

British Journal of Haematology, 2000, 108, 689–695

Early haemorrhagic morbidity and mortality during remission induction with or without all-*trans* retinoic acid in acute promyelocytic leukaemia

Eros Di Bona,[1] Giuseppe Avvisati,[2] Giancarlo Castaman,[1] Maria Luce Vegna,[2] Vitaliana De Sanctis,[2] Francesco Rodeghiero[1] and Franco Mandelli[2] for the Gruppo Italiano per le Malattie Ematologiche

	AIDA (n = 499)	IDA only (n = 123)	P
Overall mortality	38 (7.6%)	20 (16.2%)	<0.003
Haemorrhagic deaths*	15 (3%)	5 (4.1%)	n.s.
Haemorrhagic score**	2 ± 2.7	3.4 ± 3.6	<0.001
Platelet concentrate/Units (median*)	12	31	<0.001
pRBC (units), median*	2	4	<0.001

* In the first 10 days
** In the first 5 days (min. 0 - max. 15)

ADDITIONAL RISK FACTORS FOR BLEEDING IN LEUKEMIA PATIENTS

- Fever
- DIC
- Minor bleeds
- Amphotericin B administration
- Anemia

RISK FACTORS FOR BLEEDING IN APL

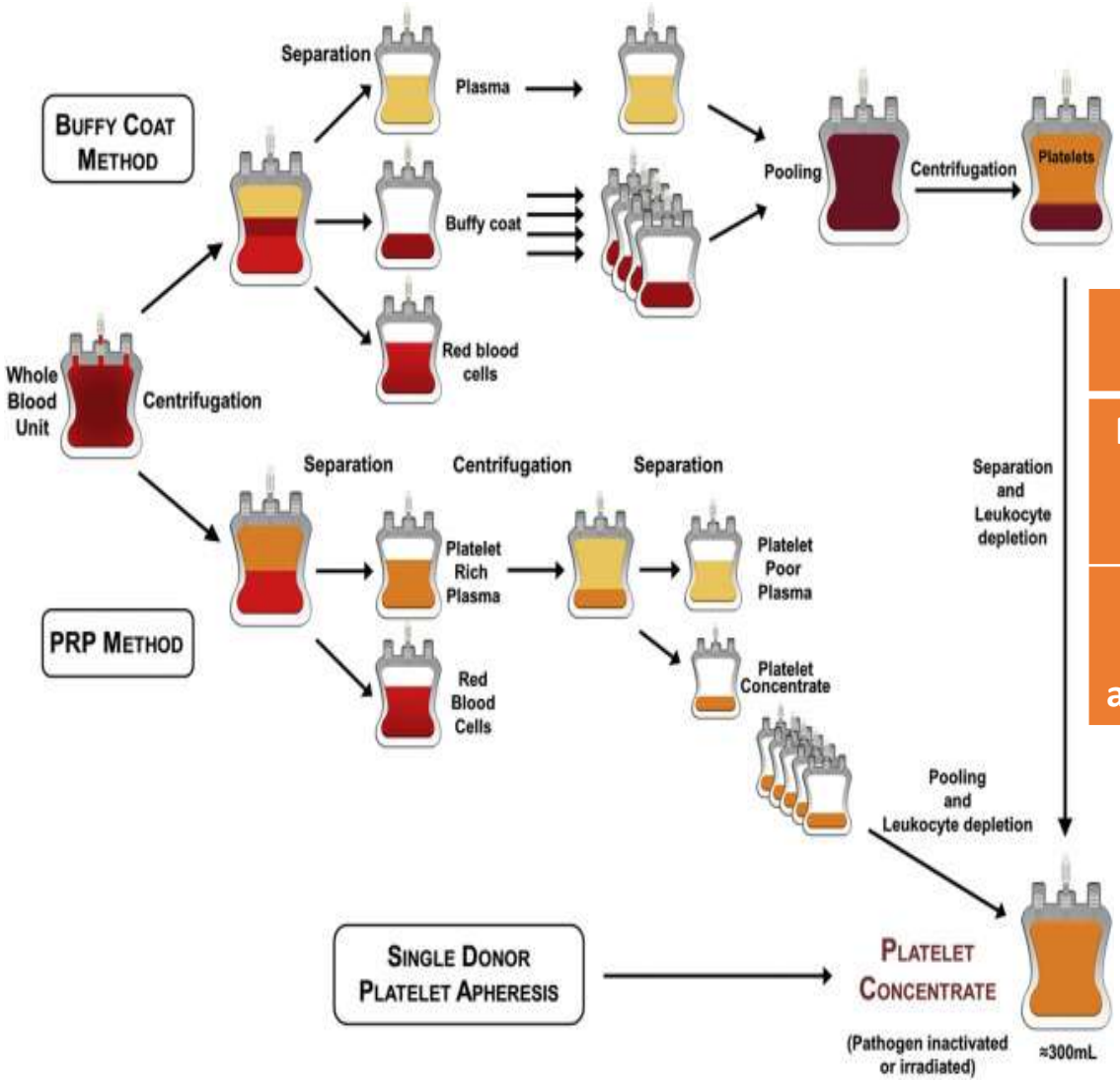
- High blast cell count
- Low fibrinogen
- Creatinine level
- Delayed start of ATRA treatment

Webert KE, et al. Haematologica 2006; 91: 1530-1537; Rebulla P, et al. N Engl J Med 1997; 337: 1870-1875; Breccia M, Lo Coco F. Thromb Res 2014;133 Suppl 2:S112-116.

BLEEDING TREATMENT

- In case of an active bleeding in patients with cancer related thrombocytopenia, **platelet transfusion** is the first line of therapy if bleeding is considered related to thrombocytopenia

PLATELET CONCENTRATES



	platelets /unit	Volume	WBC/RBC contamination
PC from BC/PRP	0.5 to 0.75 x 10^{11}	50 mL	high
Single donor apheresis	at least 3 x 10^{11}	200 mL	low

Figure from Burnouf T. et al, Biomaterials, Volume 76, January 2016, Pages 371-387

CHOOSING BETWEEN PCs AND PLATELETS FROM PA

- The amount of transfused platelets is equivalent by using one apheresis or 4-6 random PCs
- There is **no evidence** of different efficacy of platelet count recovery by using these different products, especially in patients occasionally in need of platelet support
- For cancer patients who are usually immunosuppressed and that could have low platelet count for long time, the different content in WBC should be considered
- Donor leukocytes could produce an immune response against recipient cells and lead to an allo-immunization of transfusion recipient and a transfusion associated graft versus host disease (TA-GVHD)

AB0 GROUP SELECTION FOR PLATELET TRANSFUSION

- Platelet express surface **ABO antigens**, suggesting that ABO-matched transfusion should be the best option
- If not possible, the most important feature to be considered is the presence of anti-A or anti-B antibodies present in the plasma of the PCs or PA, that could produce hemolysis in the recipient.

Recipient ABO		Component ABO		
	1st Choice	2nd Choice	3rd Choice	4thChoice
A	A	AB	B	O
B	B	AB	A	O
AB	AB	A	B	O
O	O	A	B	AB

- Platelets do not express **RhD antigen**. Attention should be paid only in RhD negative females of childbearing age who could have alloimmunization by RBCs as contaminant.

EXPECTED PLATELET COUNT INCREMENT AFTER TRANSFUSION

- The expected increase of platelet count in a patient of 70 Kg of weight after transfusion of an average amount of 3.5-4.0 X 10^{11} platelets (estimated contents of 4-6 random PCs or 1 PA) is 35,000-40,000/µL

$$\text{1-hour Corrected Count Increment (CCI)} = \frac{\text{absolute increment of platelet count x body-surface area } (m^2)}{\text{number of platelets transfused x } 10^{11}}$$

- Expected CCI is about 15,000/µL X 10^{11} platelets transfused per square meter of body surface area

Efficacy assessment and platelets transfusion criteria
(18 Italian Centers, 2,396 patients, 23,162 platelet transfusions)

Efficacy assessment (Plts count)	
After 1 hour	2 (11%)
After 24 hours	16 (89%)
Never	2 (11%)
CCI (correct count increment)	
Yes after 1 hour	2 (11%)
Yes after 24 hours	5 (28%)
Only empirically	12 (67%)
Never	2 (11%)
Platelet transfusion in patients defined refractory	
PLT ≤10,000/μL	3 (15%)
PLT between 10 - 20,000/μL	2 (10%)
PLT ≤20^9/μL	1 (5%)
Only in the case of bleeding	14 (70%)

Tagariello et al, WP GIMEMA, 2017

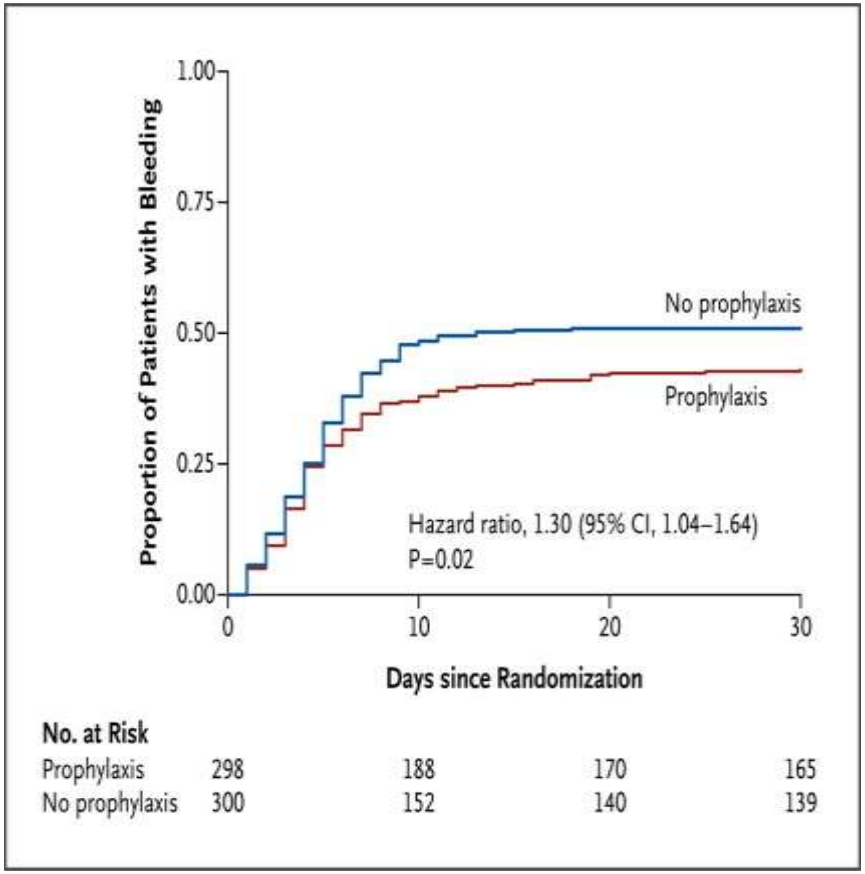
BLEEDING TREATMENT

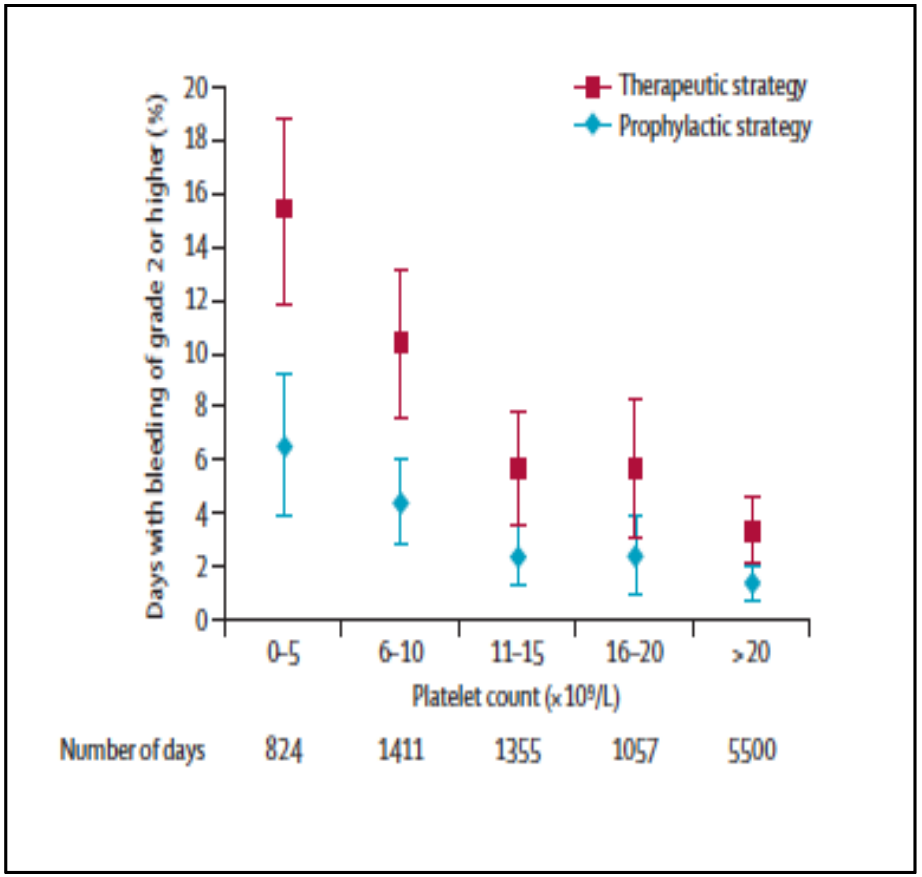
- In case of an active bleeding in patients with cancer related thrombocytopenia, **platelet transfusion** is the first line of therapy if bleeding is considered related to thrombocytopenia

- Prophylaxis → Which Threshold?

- On Demand

BLEEDING PROPHYLAXIS IN ASYMPTOMATIC THROMBOCYTOPENIC PATIENTS



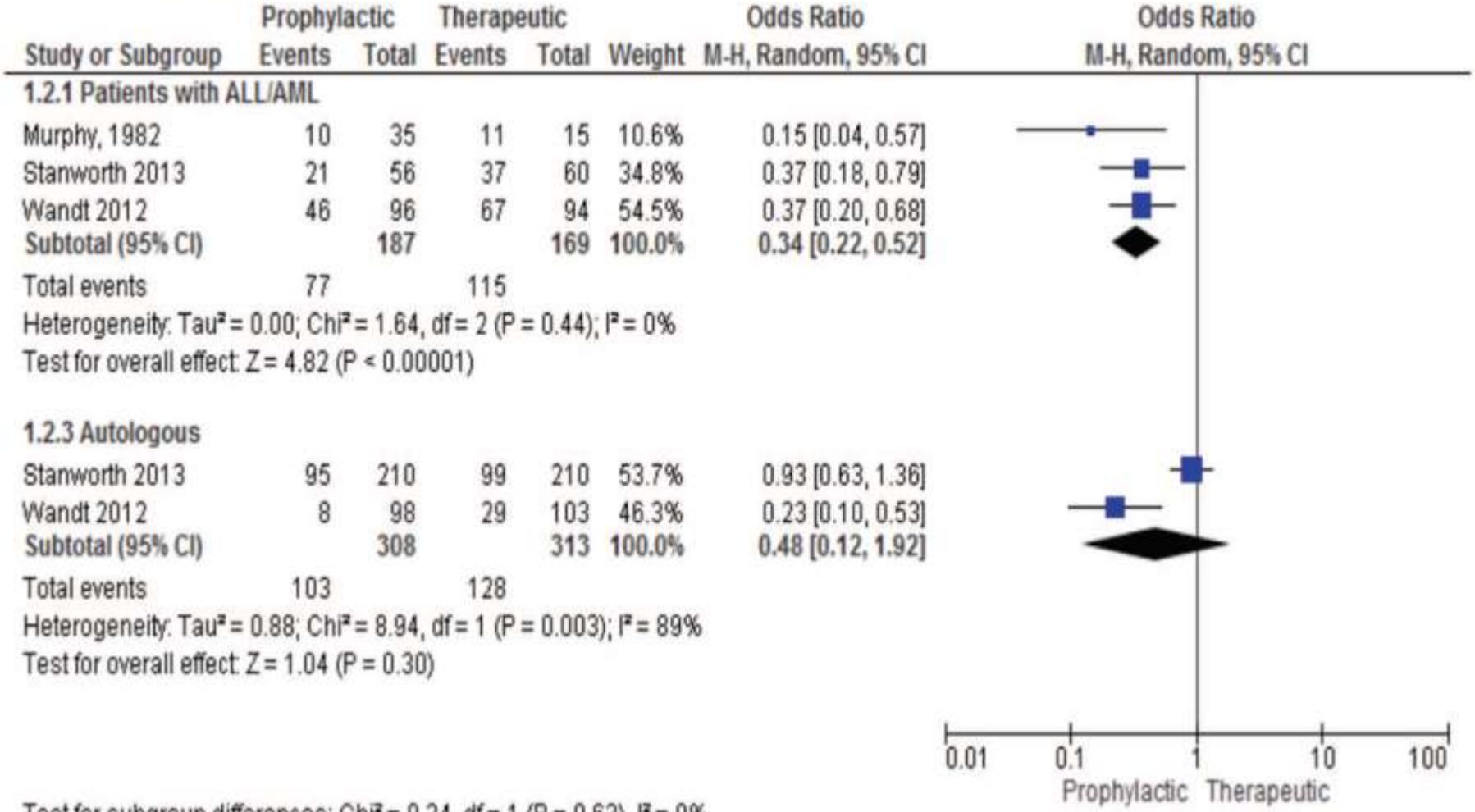


Stanworth SJ et al. N Engl J Med 2013; 368: 1771

Wandt H et al. Lancet 2012; 380: 1309

ICTHIC

Number of participants with a clinically significant bleeding event (WHO grade ≥ 2): Disease subgroups

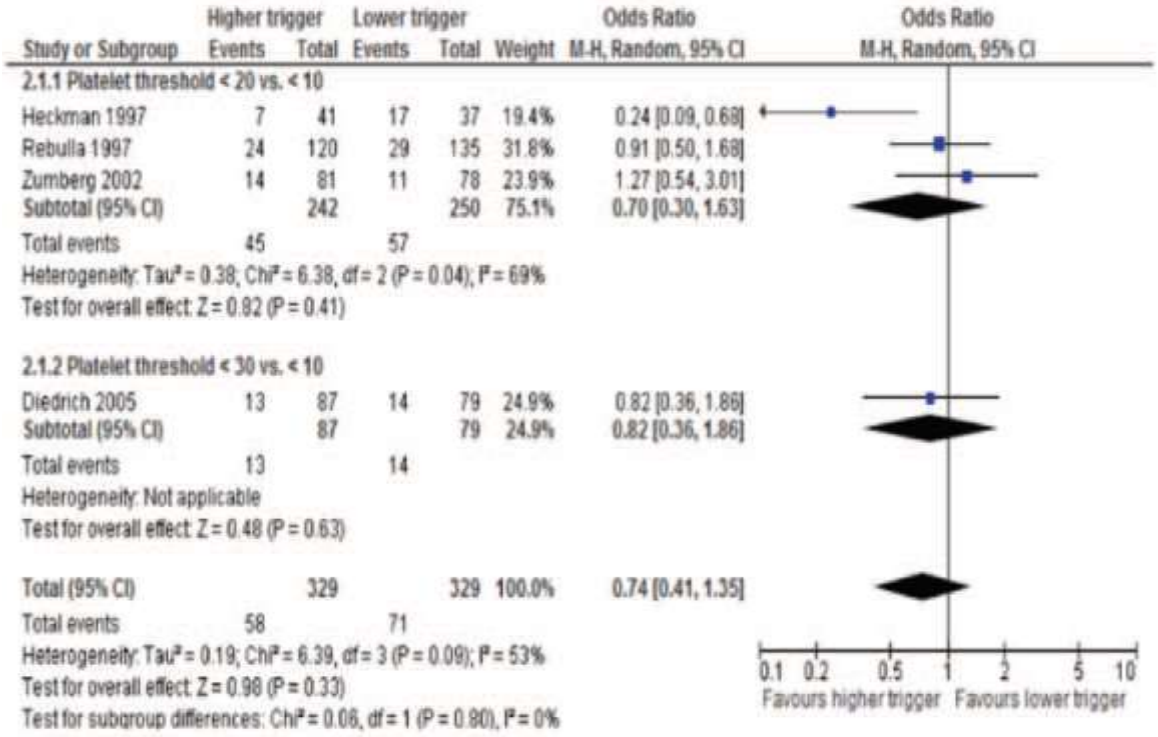


Fasano RM, Josephson CD. Hematology 2015;2015:462

THRESHOLD FOR PROPHYLACTIC PLATELET TRANSFUSION

- No differences in the likelihood of hemorrhages occurred between low, standard and high dose regimen
- **The lowest threshold of 10,000/µL** is suggested in order to reduce the risk of allo-immunization and the costs

Number of participants with major bleeding



Fasano RM, Josephson CD. Hematology 2015;2015:462

VOLUME 36 · NUMBER 3 · JANUARY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Charles A. Schiffer, Kari Bohlke, Meghan Delaney, Heather Hume, Anthony J. Magdalinski, Jeffrey J. McCullough, James L. Omel, John M. Rainey, Paolo Rebulla, Scott D. Rowley, Michael B. Troner, and Kenneth C. Anderson

- Prophylactic platelet transfusion should be administered to hospitalized adult patients with therapy-induced hypo-proliferative thrombocytopenia and a platelet count ≤ 10×10^9/L or less to reduce the risk for spontaneous bleeding. (Grade: strong recommendation; high quality evidence)

Platelet Transfusion Threshold in Patients With Solid Tumors

UPDATED. The risk of bleeding in patients with solid tumors during chemotherapy-induced thrombocytopenia is related to the depth and duration of the platelet nadir, although other factors contribute as well. The Panel recommends a threshold of $< 10 \times 10^9$/L for prophylactic platelet transfusion, based on extrapolation from studies in hematologic malignancies. Platelet transfusion at higher levels is appropriate in patients with active localized bleeding, which can sometimes be seen in patients with necrotic tumors (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical and laboratory data for platelet transfusion criteria during 2013 in Italy (18 Departments of Hematology)

Patients undergoing to HDCHT/BMT	2,396
PCs transfused per HDCHT/BMT (ratio)	3.9
Total transfused PCs	23,162
Cut off of platelets for transfusion	
Always with PLT ≤ $10x10^9$/L	17 (95%)
In symptomatic patients with PLT between $10x10^9$/L and $20x10^9$/L	13 (72%)
Always with PLT ≤ $20x10^9$/L	1(5%)
Definition of "symptomatic"	
Fever >38°	13 (72%)
All bleeding	11 (61%)
According to WHO bleeding score (WHO≥2)	6 (33%)

Tagariello et al, WP GIMEMA, 2017

Prevention and Management of bleeding in APL

MAINSTAYS of TREATMENT:

- Start ATRA, just in suspect
- Platelet transfusion, to maintain plt > $50x10^9$/L (also twice daily)
- Delay CVC insertion
- Red Blood cell transfusion, to maintain Hb > 8g/dL
- If cerebral bleeding is suspected:
  - Perform CT scan or MRI immediately
  - Avoid lumbar puncture
  - Intensive Care Unit

REFRACTORINESS TO PLATELET TRANSFUSION

CCI $<7.5 \times 10^9$/L after 1 hour
or
CCI $<4.5 \times 10^9$/L after 24 hours

After at least two platelet transfusions with ABO-matched products stored for less than 72 hours

- **Alloimmunization against HLA antigens** occurs in about 25-35% patients with new diagnosis of acute myeloid leukemia (AML) receiving random PCs
- Up to 18 % of patients become HLA alloimmunized and 3 % develop immune-mediated platelet refractoriness notwithstanding the preventive approach.
- To be considered: consumption due to active bleeding, fever, drugs (e.g. amphotericin B), micro-angiopathies or DIC and splenomegaly.

MEASURES TO REDUCE THE RISK OF REFRACTORINESS

- Platelet Apheresis should be preferred due to lower WBC number
- If PA is not available, PCs must be filtered to reduce the number of leukocytes

TREATMENT OF PATIENTS REFRACTORY TO PLATELET TRANSFUSION

HLA –matched products

TRANSFUSION-ASSOCIATED GRAFT VERSUS HOST DISEASE (TA-GVHD)

- Immune response against recipient cells produced by donor leukocytes

- The prevention of TA-GVHD requires the irradiation of PCs or AP, usually performed with gamma rays that produce leukocyte DNA damage.

- The conditions with an high risk of TA-GVHD are represented by heavy immunosuppression, like hematopoietic stem cells transplantation (HSCT) and hematological malignancies.

Blood Transfusions, Thrombosis, and Mortality in Hospitalized Patients with Cancer

Khorana et al. Arch Intern Med 2008

- **Retrospective cohort study by discharge database**

- 504,208 patients:

  - 70,542 patients (14%) received at least 1 RBC transfusion
  - **15,237 patients (30%) received at least 1 platelet transfusion**

- During follow-up:

  - 7.2% patients receiving RBC transfusions developed DVT
  - 3.8 % non-transfused patients

  - 5.2% patients developed arterial thromboembolism (ATE)
  - 3.1 % non-transfused patients

Blood Transfusions, Thrombosis, and Mortality in Hospitalized Patients with Cancer

Khorana AA et al. Arch Intern Med 2008

Transfusions	Odds Ratio (95% CI) Venous thromboembolism	Odds Ratio (95% CI) Arterial thromboembolism	P Value vs non-transfused
Red blood cell only	1.60 (1.53-1.67)	1.53 (1.46 – 1.61)	<.001
Platelets only	1.20 (1.11-1.29)	1.55 (1.40 – 1.71)	<.001

Transfusions were also associated with an **increased risk of in-hospital mortality** (**RBCs: OR, 1.34;** 95% CI, 1.29-1.38; **Platelets: 2.40**; 2.27-2.52; P<.001)

Both RBC and platelet transfusions are associated with increased risks of venous and arterial thrombotic events and mortality in hospitalized patients with cancer

ICTHIC

Platelet Transfusion and Thrombosis: More Questions than Answers

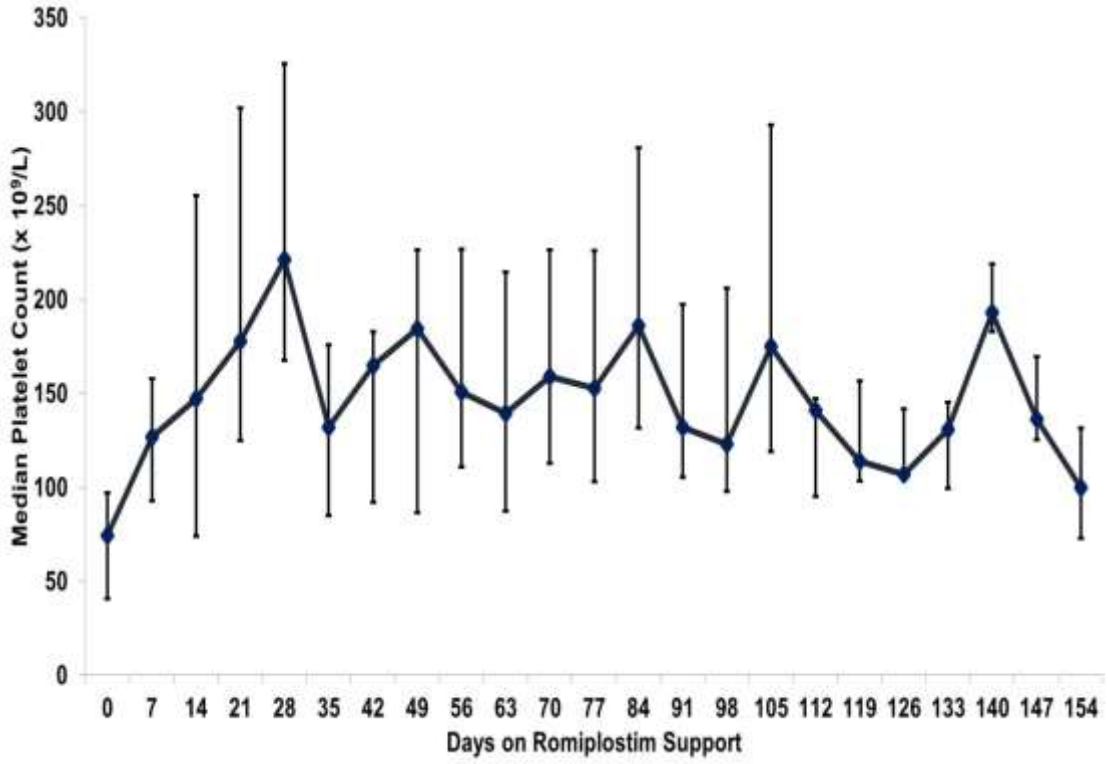
Amy E. Schmidt, MD, PhD[1] Majed A. Refaai, MD[1] Neil Blumberg, MD[1]

Semin Thromb Hemost 2016;42:118–124.

- Platelet microparticles have 50-100-fold higher procoagulant activity than activated whole platelets (Sinauridze et al, 2007)
- High PMPs in cancer patients (Goubran et al, 2015)
- Relevant role of PMPs in thrombus formation and restoring reduced thrombin generation (Matijevic et al, 2011)
- TTP and HIT patients who receive platelet transfusion have an increased risk of arterial thrombosis and mortality (Goel et al, 2015)

ALTERNATIVE TREATMENTS FOR THROMBOCYTOPENIA IN CANCER: TPO-mimetics

Median weekly platelet counts during chemotherapy for a solid tumor in a cohort of 22 patients on **romiplostim** support.

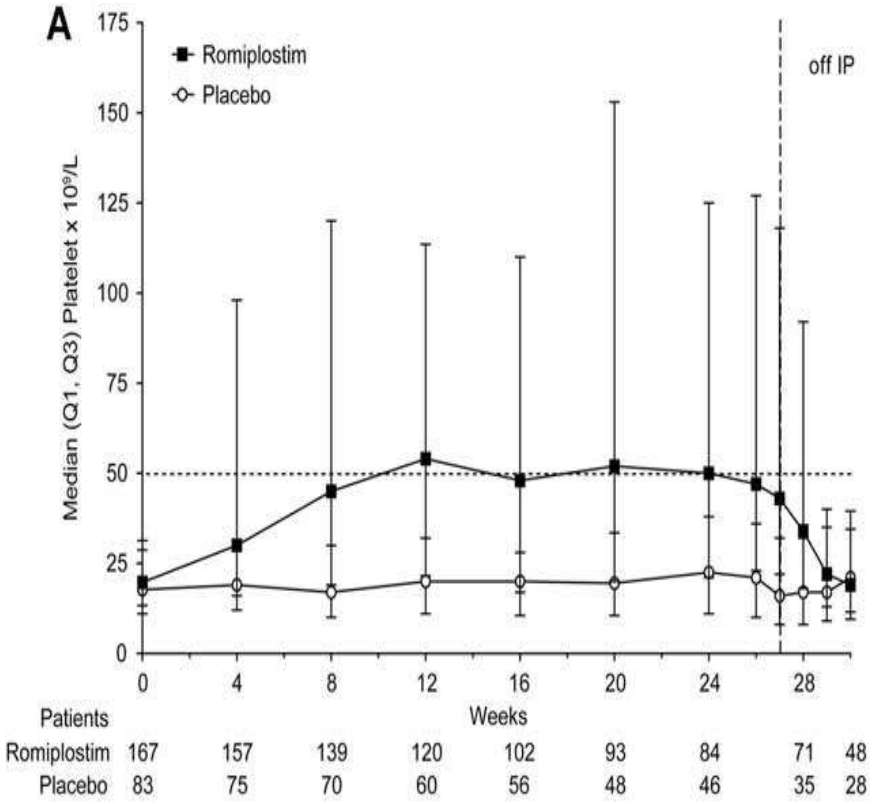


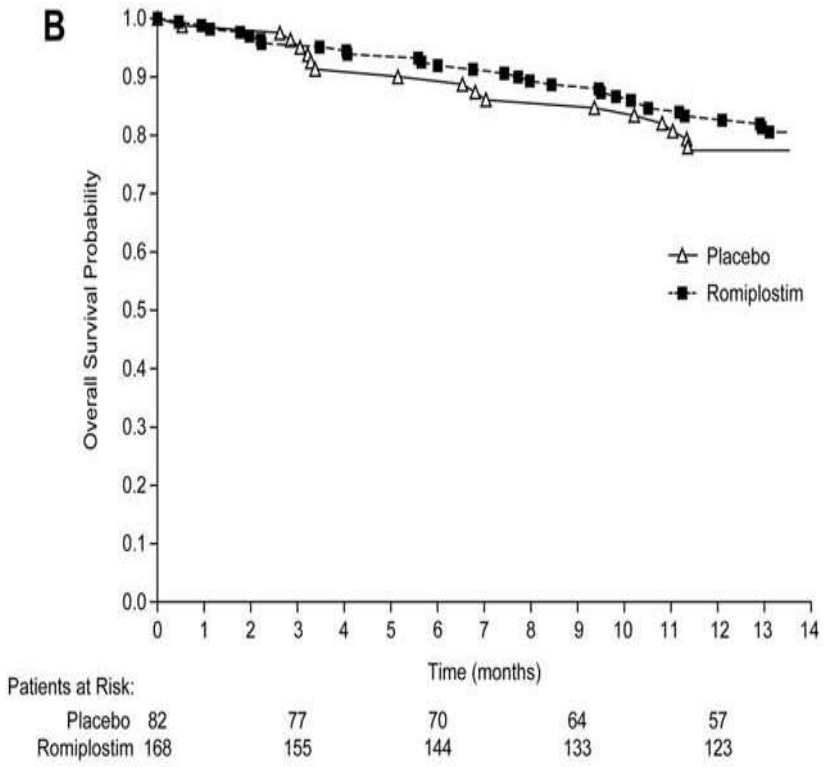
- Romiplostim may significantly reduce chemotherapy delay and dose-reduction due to thrombocytopenia in cancer patients
- No uniform standard in oncology practice as to when chemotherapy dosage should be adjusted or held to avoid thrombocytopenia and bleeding
- There is no consensus defining a "safe" platelet count during chemotherapy and no evidence that correction of a "low" platelet count affects survival.

Al-Samkari H, et al. Haematologica. 2017; 102:xxx, doi:10.3324/haematol.2017.180166

ROMIPLOSTIN IN MDS

Phase III Low-Intermediate-1–Risk Myelodysplastic Syndrome and Thrombocytopenia

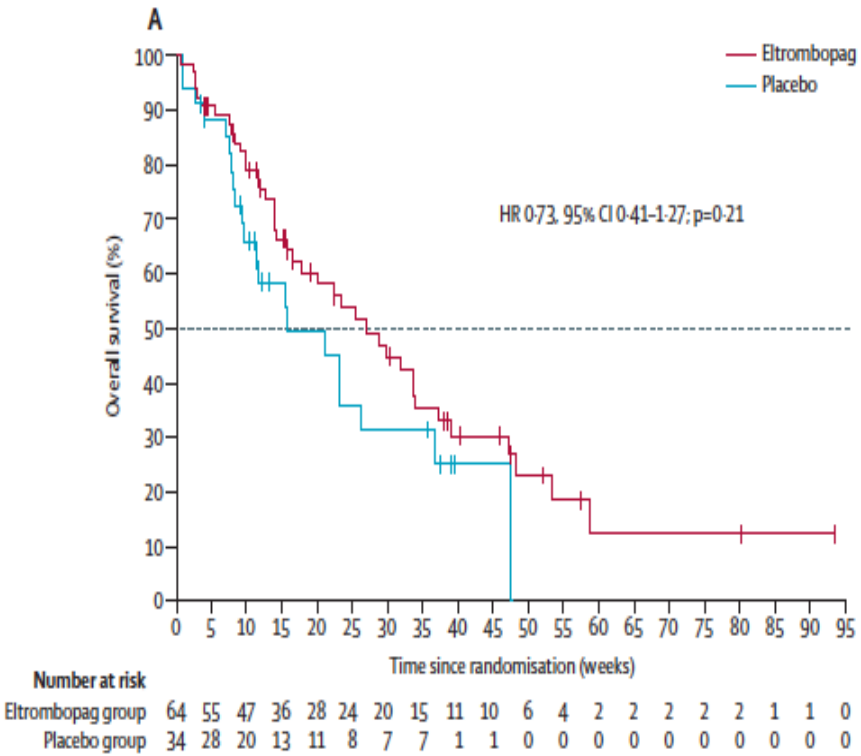


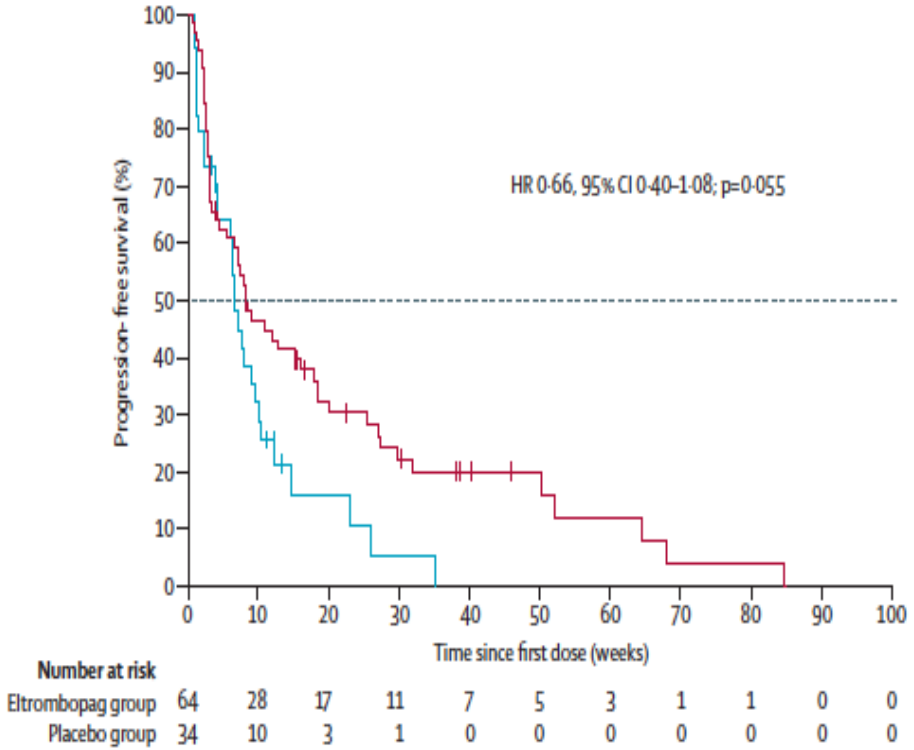


Giagounidis A, et al. Cancer 2014;120: 1838-46

ELTROMBOPAG IN MDS

phase 1-2 trial in patients with
advanced MDS and AML with thrombocytopenia





Platzbecker U, et al. Lancet Haematol 2015; 2: e417-426.

Antithrombotic treatment in thrombocytopenic cancer patients

- Thrombotic events are frequent in cancer patients and of major concern especially during or prior to chemotherapy

- The safe levels of platelet count to adapt the most appropriate anticoagulant dose is still undetermined

- Anticoagulant treatment is often reduced/withheld for fear of bleeding and/or chemotherapy delayed because of concerns about progression of VTE

Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and VTE: an expert consensus

Napolitano MS ; **G**ruppo **I**taliano **M**alattie **EM**atologiche dell'**A**dulto (GIMEMA) Working Party on Thrombosis and Hemostasis

- In **acute VTE**, safe anticoagulation with LMWH at therapeutic doses for platelet count between $\geq 50 < 100 \times 10^9$/L and at 50% dose reduction for a platelet count of $\geq 30 < 50 \times 10^9$/L is recommended

- The discontinuation of LMWH treatment is recommended for a platelet count of $< 30\times 10^9$/L

- In **acute VTE**, Inferior Vena Cava (IVC) filter positioning and prophylactic LMWH administration is recommended for platelet count $< 30\times 10^9$/L

Conclusions

- Platelet transfusion remains the cornerstone of treatment for thrombocytopenia-associated bleeding in cancer
- The criteria for and clinical role of prophylactic platelet transfusions are clearly established for patients with blood malignancies
- In patients with solid tumors, these criteria are still ill-defined and platelet transfusions should be used judiciously according to the presence of comorbidities
- Alternative treatments with TPO-mimetics for these patients seem promising, but the best timing is still unknown
- Further studies about the best ways to prevent and treat refractoriness are required

Total number, source and ABO compatibility of PCs transfused in 18 Italian HDs during 2013

Total PCs (average 1,287/center, range 300-4,100)	**23,162**
Type of concentrate	
Pool	**38%**
Apheresis	**62%**
ABO compatibility	
Yes	**4 (25%)**
No	**3 (20%)**
Partially	**11 (55%)**

Tagariello et al, WP GIMEMA, 2017