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# Anaemia and thrombocytopenia caused by cancer and anticancer treatment: how to prevent and manage best?


Matti Aapro, MD
Genolier, Switzerland
Member European Society for Medical Oncology (ESMO)
Supportive Care Faculty
Past President of the Multinational Association for Supportive Care in Cancer (MASCC)
And Honorary President of AFSOS
(French-speaking Association for Supportive Care)
And Consultant to JASCC ( Japanese Association for Supportive Care in Cancer)

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# The 2018 ESMO Anaemia Guideline


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# DISCLOSURE OF INTEREST

## Dr. Matti Aapro

Consultant to

Accord, Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, JnJ, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor

and has received honoraria for lectures at symposia of

Accord, Amgen, Bayer Schering, Biocon, Boehringer, Cephalon, Chugai, Eisai, DrReed, Genomic Health, Glenmark, GSK, Helsinn, Hospira, Ipsen, JnJ, OrthoBiotech, Kirin Kyowa, Merck, Merck Serono, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor

# Disclosures

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

MASCC
MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER

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www.afsos.org

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- Collaborations in this field: Teva, Sandoz, Roche, Novartis, JnJ, Hospira, Amgen, DRL, Pierre Fabre

**CLINIQUE DE GENOLIER**

ONLINE February 2018
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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

*Annals of Oncology* 0: 1–15, 2018
doi:10.1093/annonc/mdx758

CLINICAL PRACTICE GUIDELINES

# Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines†

M. Aapro[1], Y. Beguin[2,3], C. Bokemeyer[4], M. Dicato[5], P. Gascón[6], J. Glaspy[7], A. Hofmann[8], H. Link[9], T. Littlewood[10], H. Ludwig[11], A. Österborg[12], P. Pronzato[13], V. Santini[14], D. Schrijvers[15], R. Stauder[16], K. Jordan[17] & J. Herrstedt[18,19], on behalf of the ESMO Guidelines Committee*

# Erythropoiesis-Stimulating Agents in the Treatment of Anaemia in Cancer Patients: ESMO Clinical Practice Guidelines for Use

clinical practice guidelines

*Annals of Oncology* 21 (Supplement 5): v244–v247, 2010
doi:10.1093/annonc/mdq202

## Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use

D. Schrijvers[1], H. De Samblanx[1] & F. Roila[2]
On behalf of the ESMO Guidelines Working Group*

[1]*Department Hemato-Oncology, Ziekenhuisnetwerk Antwerpen-Middelheim, Antwerp, Belgium;* [2]*Department of Medical Oncology, Santa Maria Hospital, Terni, Italy*

Schrijvers D, et al. *Ann Oncol.* 2010;21(suppl 5):v244-v247.

# EORTC Guidelines for Erythropoietic Proteins in Anaemic Patients with Cancer

EUROPEAN JOURNAL OF CANCER 43 (2007) 258–270

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com


Review

## EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update

C. Bokemeyer[a,*], M.S. Aapro[b], A. Courdi[c], J. Foubert[d], H. Link[e], A. Österborg[f], L. Repetto[g], P. Soubeyran[h]

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[h]Institut Bergonié, 229 Cours de l'Argonne, F-33076 Bordeaux, France

Bokemeyer *et al*. *Eur J Cancer*. 2007;43:258–270

# Impact of Erythropoietin or Darbepoetin on Quality of Life

Overall, there is a statistically significant difference between patients treated with ESAs and controls when combining QOL parameters and fatigue- and anemia-related symptoms, which is however, most likely not clinically important.

Tonia T, et al. *Cochrane Database Syst Rev.* 2012;12:CD003407.

# Risks and Benefits of RBC Transfusions

| | RBC Transfusions |
|---|---|
| Risks | ■ Transfusion reactions (eg, hemolytic, febrile, nonhemolytic, lung injury)<br>■ Transfusion-associated circulatory overload<br>■ Virus transmission (eg, hepatitis, HIV)<br>■ Bacterial contamination<br>■ Iron overload<br>■ **Increased thrombotic events**<br>■ **Possible decreased survival** |
| Benefits | ■ Rapid increase in Hb and hematocrit levels<br>■ Rapid improvement in anemia-related symptoms |

HIV = human immunodeficiency virus

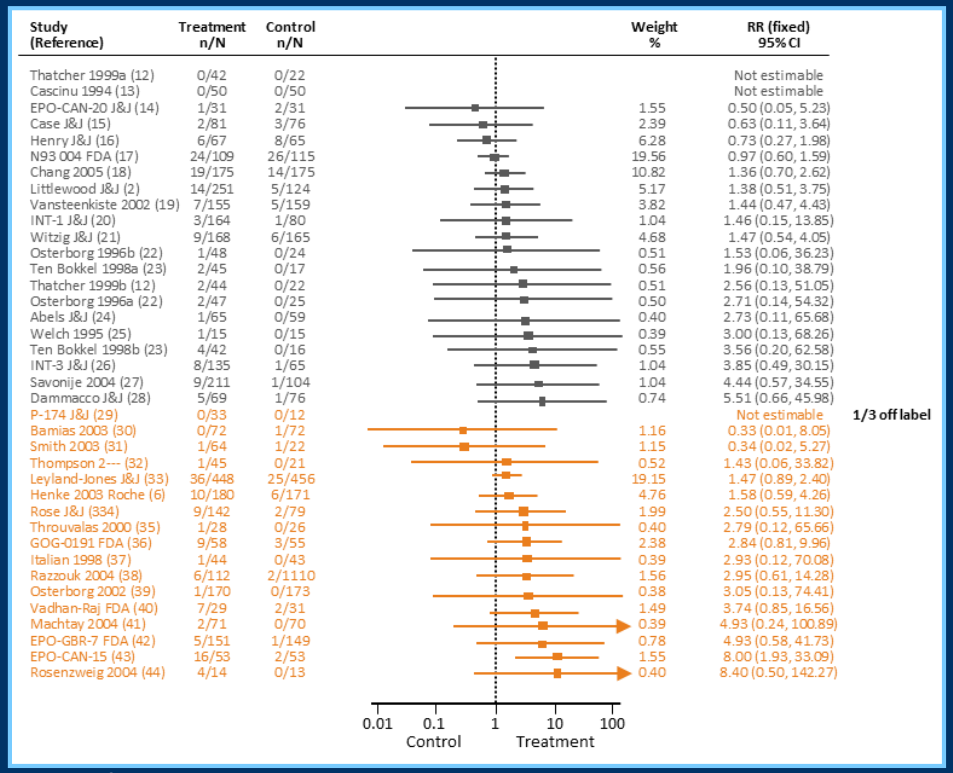
NCCN Clinical Practice Guidelines in Oncology. Cancer- and chemotherapy-induced anemia. Version 2. 2015.

# Safety of ESAs
## *Thromboembolic Events*

- VTEs are frequent in patients with cancer because of the effects of malignant disease, its treatment and associated comorbidities, and TRANSFUSIONS[1]
- Use of ESAs is associated with a higher risk of VTEs[1]
  - This may be particularly pronounced when ESAs are used in patients without anemia at baseline and/or to achieve Hb targets higher than those recommended in current labeling

If the goal of treatment for patients with chemotherapy-associated anemia is to raise the Hb level to 12 g/dL, and it is confined to that, ESA-induced VTEs should rarely be a problem[1]

**Meta-analysis of RR for thromboembolic complications in patients with cancer receiving ESAs or standard care[1]**




CI = confidence interval; RR = relative risk; VTE = venous thromboembolic event


1. Dicato M. *Oncologist*. 2008;13(suppl 3):11-15.
2. Tonia T, et al. *Cochrane Database Syst Rev.* 2012;12:CD003407.

# KEY POINTS

# Guidelines for Treatment of Anaemia in Patients with Cancer

The major aims of anaemia management are

the reduction or resolution of anaemia symptoms,

particularly fatigue and an improved QoL

with the minimum invasive treatment
that corrects the underlying causes and proves to be safe.

Annals of Oncology, https://doi.org/10.1093/annonc/mdx758

# Guidelines for the Treatment of Anemia in Patients With Cancer

- Additional causes of anemia should be corrected prior to erythropoietic protein therapy
- …… iron deficiency (absolute or functional), bleeding, vitamin B12 or folate deficiency, nutritional defects or hemolysis

Annals of Oncology, https://doi.org/10.1093/annonc/mdx758

Already in Schrijvers D, et al. *Ann Oncol.* 2010;21(suppl 5):v244-v247.

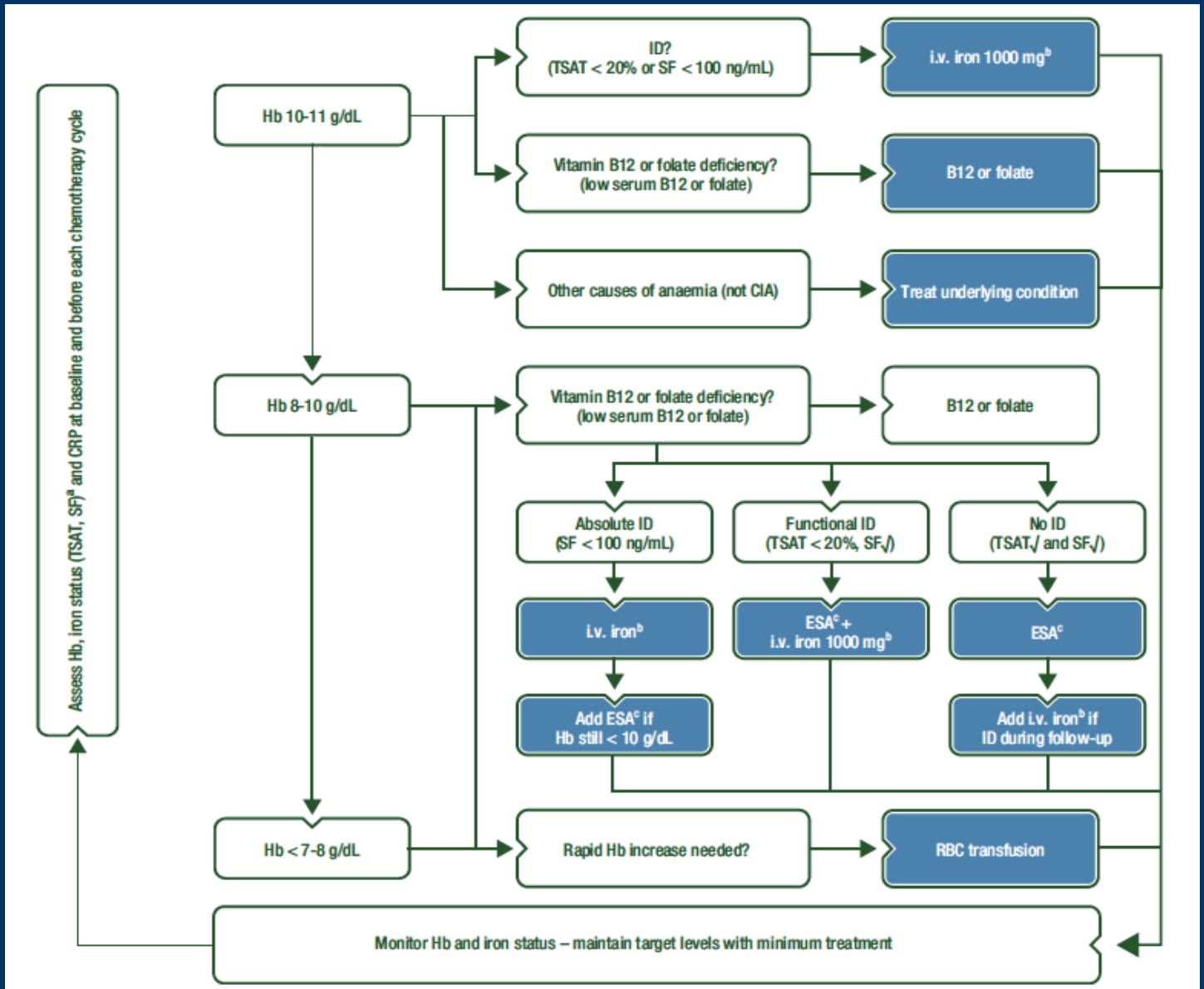
# Guidelines for Treatment of Anaemia in Patients with Cancer

- Hb target of ESA therapy is a stable level of about 12 g/dL without RBC transfusions.

  modified from should be 12 to 13 g/dL

Annals of Oncology, https://doi.org/10.1093/annonc/mdx758

# Annals of Oncology, https://doi.org/10.1093/annonc/mdx758



# Guidelines for Treatment of Anaemia in Patients with Cancer

Annals of Oncology, https://doi.org/10.1093/annonc/mdx758

reviews

Annals of Oncology

*Annals of Oncology* 23: 1954–1962, 2012
doi:10.1093/annonc/mds112
Published online 9 May 2012

## Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron

M. Aapro[1]*, A. Österborg[2], P. Gascón[3], H. Ludwig[4] & Y. Beguin[5]

*[1]IMO Clinique de Genolier, Genolier, Switzerland; [2]Department of Hematology, Karolinska Institutet and Karolinska Hospital, Stockholm, Sweden; [3]Department of Haematology-Oncology, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain; [4]Department of Medicine I, Center for Oncology and Haematology, Wilhelminenspital, Vienna, Austria; [5]Department of Medicine, Division of Hematology, University Hospital Liège, Liège, Belgium*

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Critical Reviews in Oncology/Hematology 89 (2014) 1–15

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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## Epidemiological and nonclinical studies investigating effects of iron in carcinogenesis—A critical review☆

Yves Beguin [a,*], Matti Aapro [b], Heinz Ludwig [c], Lee Mizzen [d], Anders Österborg [e]

[a] *University Hospital Liège, Belgium*
[b] *IMO Clinique de Genolier, Switzerland*
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[e] *Karolinska Institutet and Karolinska Hospital, Stockholm, Sweden*

Accepted 31 October 2013

## Guidelines for Treatment of Anaemia in Patients with Cancer

- In patients with Hb <7-8 g/dL and/or severe anaemia related symptoms (even at higher Hb levels) and the need for immediate Hb and symptom improvement, the administration of RBC transfusions without delay is justified.

Annals of Oncology, https://doi.org/10.1093/annonc/mdx758

Overall,
there is currently no clinical evidence
(neither single studies nor meta-analyses)
indicating an effect of ESAs on stimulating
disease progression or relapse
when used within label and following
recommendations for the treatment of
chemotherapy-induced anaemia [I, A]

Annals of Oncology, https://doi.org/10.1093/annonc/mdx758

## ABOUT BIOSIMILARS

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Guidelines for Treatment of Anaemia in Patients with Cancer

**MDS updated in the recommendations**
**Based on existing ESMO guideline**

clinical practice guidelines

*Annals of Oncology* 25 (Supplement 3): iii57–iii69, 2014
doi:10.1093/annonc/mdu180
Published online 25 July 2014

# Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

P. Fenaux[1], D. Haase[2], G. F. Sanz[3], V. Santini[4] & C. Buske[5] on behalf of the ESMO Guidelines Working Group*

*[1]Service d'Hématologie Clinique, Groupe Francophone des Myélodysplasies (GFM), Hôpital St Louis (Assistance Publique, Hôpitaux de Paris) and Paris 7 University, Paris, France; [2]Clinics of Hematology and Medical Oncology, University Medicine, Goettingen, Germany; [3]Department of Haematology, Hospital Universitario y Politécnico La Fe, Valencia, Spain; [4]Functional Unit of Haematology, AOU Careggi, University of Florence, Firenze, Italy; [5]Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital, Ulm, Germany*

Saturday at this course:

11:25-11:45 EPO and thrombopoietic agents in MDS **V. Santini**

# From ESMO 2018 GUIDELINES

In symptomatic patients treated with chemotherapy and an Hb level of <10 g/dl, treatment with ESAs might be considered to increase Hb to ≤ 12 g/dl.

Treatment recommendations according to label can be followed if there is no suspicion of functional iron deficiency (ferritin >100 ng/ml and TSAT <20%).

MDS has been added

17th Annual Course on "Anaemia, Neutropenia, Thrombosis and Cancer"
Vienna, Austria

# New developments for thrombocytopenia management, ITP included

**Cihan Ay, MD**

**Associate Professor**

Clinical Division of Haematology and Haemostaseology,

Department of Medicine I, Comprehensive Cancer Center Vienna,

Medical University of Vienna, Vienna, Austria



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# Conflicts of interest

- No conflicts of interest to declare.

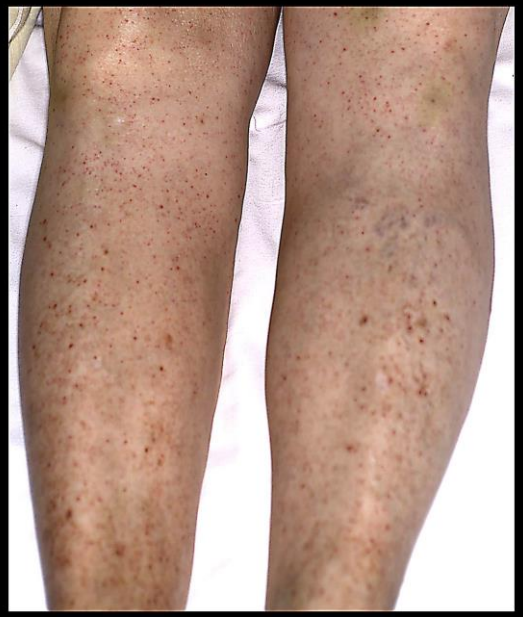
# Thrombocytopenia - What is a low platelet count?

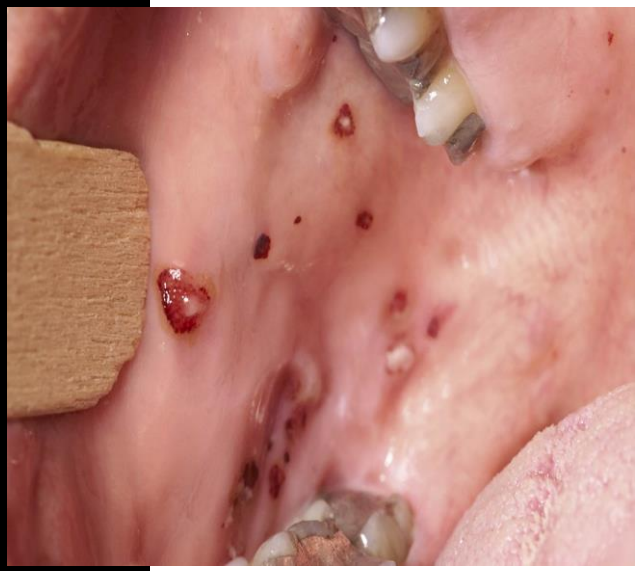
- Defined as platelet count below lower limit of normal (<150.000/µl for adults)
  - Degree of thrombocytopenia
    - Mild (100.000 - 150.000/µl)
    - Moderate (50.000 – 99.000/µl)
    - Severe (<50.000/µl)

- When to worry about bleeding?
  - Concern of bleeding in severe thrombocytopenia
    - Correlation between platelet count and bleeding risk is uncertain, and depends on the disorder and patient
    - Surgical bleeding generally may be a concern with platelet count <50.000/µl (<100.000/µl for some high-risk procedures such as neuro-, major cardiac or orthopedic surgery)
    - Spontaneous bleeding most likely with platelet count <20.000 - 30.000/µl, especially <10.000/µl)

- Patients with thrombocytopenia may be at risk of thrombosis (e.g. HIT, Antiphospholipid syndrome, DIC, TTP)

# Signs and symptoms in thrombocytopenia





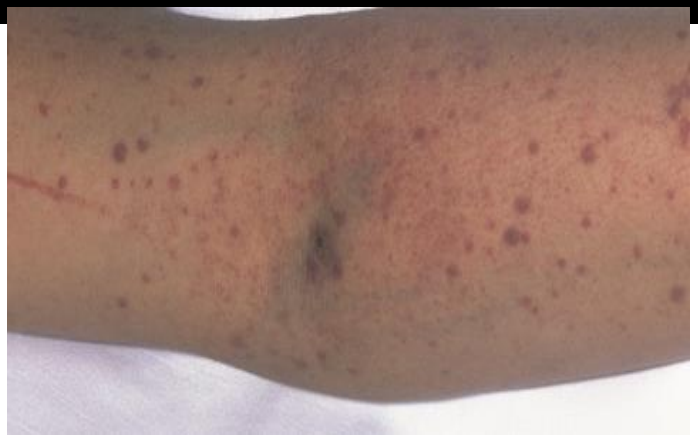


*Table 2.* Summary of the Modified WHO Bleeding Scale*

| WHO Bleeding Grade | Examples |
|---|---|
| 1 | Oropharyngeal bleeding ≤30 min in 24 h<br>Epistaxis ≤30 min in previous 24 h<br>Petechiae of oral mucosa or skin<br>Purpura ≤1 inch in diameter<br>Spontaneous hematoma in soft tissue or muscle<br>Positive stool occult blood test<br>Microscopic hematuria or hemoglobinuria<br>Abnormal vaginal bleeding (spotting) |
| 2 | Epistaxis >30 min in 24 h<br>Purpura >1 inch in diameter<br>Joint bleeding<br>Melanotic stool<br>Hematemesis<br>Gross/visible hematuria<br>Abnormal vaginal bleeding (more than spotting)<br>Hemoptysis<br>Visible blood in body cavity fluid<br>Retinal bleeding without visual impairment<br>Bleeding at invasive sites |
| 3 | Bleeding requiring red blood cell transfusion over routine transfusion needs<br>Bleeding associated with moderate hemodynamic instability |
| 4 | Bleeding associated with severe hemodynamic instability<br>Fatal bleeding<br>CNS bleeding on imaging study with or without dysfunction |

CNS = central nervous system; WHO = World Health Organization.
* From references 18 and 22.

Kaufmann RM. Ann Intern Med. 2015;162(3):205-213.

# (Chemo)Therapy-induced thrombocytopenia

- Therapy-induced hypo-proliferative thrombocytopenia (caused by a dose-dependent myelosuppressive or myeloablative chemotherapy or radiation)

- Predictable, occurs 6 – 14 days after treatment cycle and affects also other blood cell lines
  - Most frequently after chemotherapy for hematological malignancies, dose-intensive chemotherapy, palliative chemotherapy following multiple regimens

# Side effects of platelet transfusion

***Table 1.*** Approximate Per-Unit Risks for Platelet Transfusion in the United States

| Adverse Event | Approximate Risk per Platelet Transfusion | Reference |
|---|---|---|
| Febrile reaction | 1/14 | 6 |
| Allergic reaction | 1/50 | 7 |
| Bacterial sepsis | 1/75 000 | 8 |
| TRALI* | 1/138 000 | 9 |
| HBV infection | 1/2 652 580 | Personal communication† |
| HCV infection | 1/3 315 729 | Personal communication† |
| HIV infection | 0 (95% CI, 0 to 1/1 461 888) | Personal communication† |

HBV = hepatitis B virus; HCV = hepatitis C virus; TRALI = transfusion-related acute lung injury.
* The overall risk for TRALI from all plasma-containing blood products is currently estimated to be approximately 1/10 000 (10).
† Notari E, Dodd R, Stramer S.

Kaufmann RM. Ann Intern Med. 2015;162(3):205-213.

# Recommendations of American Association of Blood Banks (AABB)

**Hospitalized Adult Patients With Therapy-Induced Hypoproliferative Thrombocytopenia ( not febrile; no clinical signs of bleeding )**

- The AABB recommends that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in adult patients with therapy-induced hypoproliferative thrombocytopenia.
- The AABB recommends transfusing hospitalized adult patients with a **platelet count of 10 X $10^9$ cells/L or less** to reduce the risk for spontaneous bleeding.
- The AABB recommends transfusing up to a single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one half of a standard apheresis unit are equally effective.
- Quality of evidence: moderate; strength of recommendation: strong.

# Multiple Choice Question

- An adult patient with newly diagnosed acute myeloid leukemia (AML) receives myelosuppressive (induction or consolidation) chemotherapy and develops thrombocytopenia.

  What is the **optimal platelet count threshold for prophylactic platelet transfusion** to minimize bleeding, platelet use and adverse clinical outcomes in thrombocytopenic patients with myelosuppressive chemotherapy?

  A) ≤30 x $10^9$/L (≤30.000 platelets/µl)

  B) ≤20 x $10^9$/L (≤20.000 platelets/µl)

  C) ≤10 x $10^9$/L (≤10.000 platelets/µl)

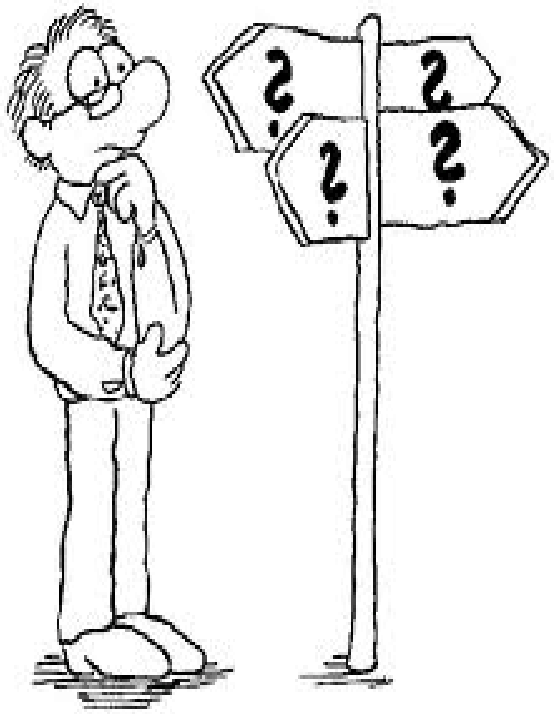
  D) ≤50 x $10^9$/L (≤50.000 platelets/µl)

  E) There is no optimal threshold defined.

# Take Home Messages

- Not platelet count alone, but the overall clinical situation determines the risk of severe bleeding in thrombocytopenic patients.
- Prophylactic platelet transfusion below a threshold of 10.000/µL (especially in acute leukemia), remains the standard in clinical routine, even though it often cannot prevent severe bleeding.
  - Daily check the patient for first signs of bleeding (more than petechiae or minimal mucosal bleeding) and administer therapeutic platelet transfusion.

# Thank you for your attention!




thank you
danke
謝謝
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teşekkür ederim
спасибо
Баярлалаа
gracias
dank je
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obrigado
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