Italian Trials in Medical Oncology

Correzione della anemia indotta o da malattia

Sandro Barni

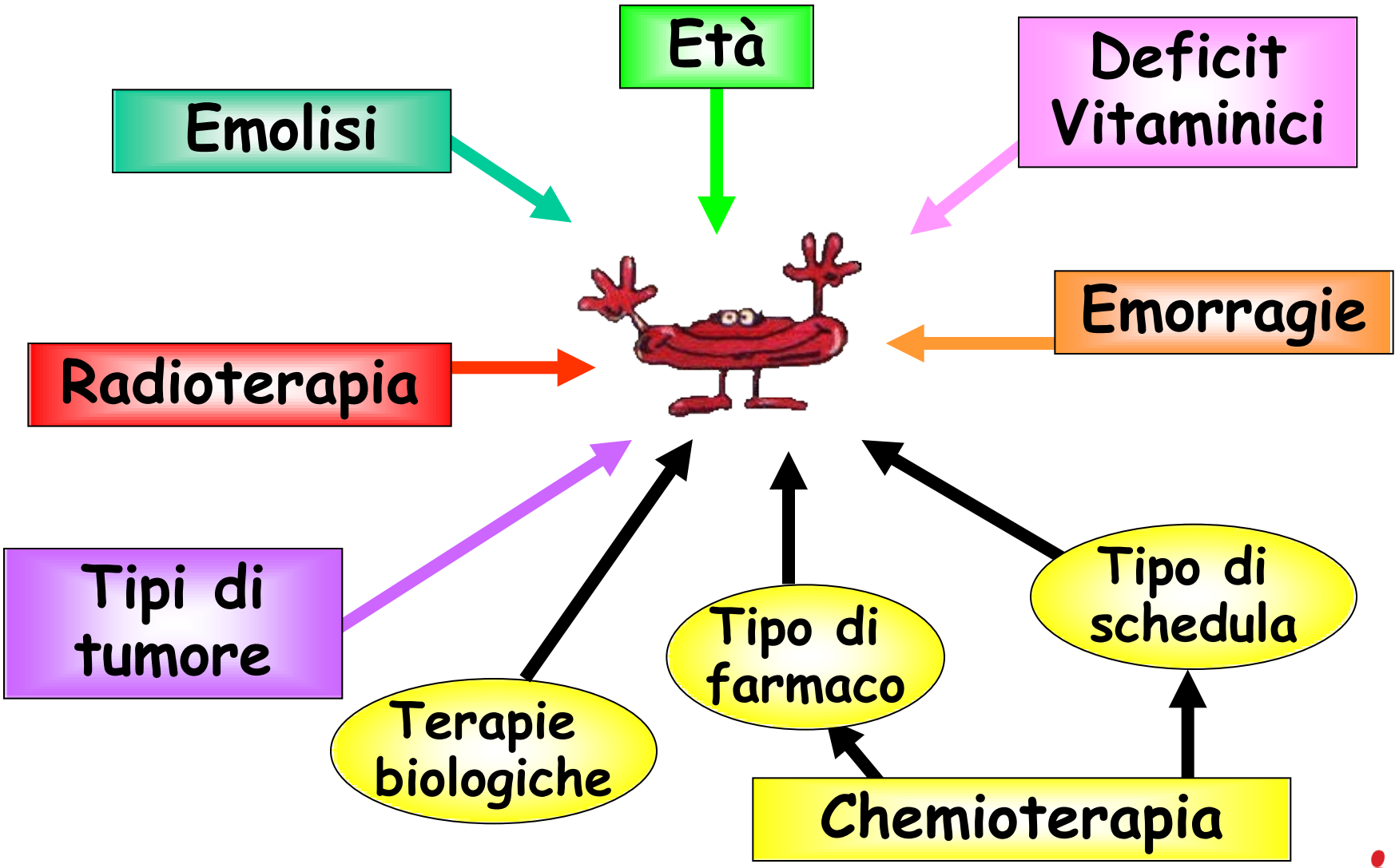
Az.Osp. Treviglio-Caravaggio

Oncologia Treviglio

Grading Anemia

	Hb	
Gravità	WHO	NCI
Grado 0 (normale)	≥ 11 g/dl	12-16 g/dl f 14-18 g/dl m
Grado 1 (lieve)	9,5-10,9 g/dl	10 g/dl
Grado 2 (moderata)	8-9,4 g/dl	8-10 g/dl
Grado 3 (grave)	6,5-7,9 g/dl	6,5-7,9 g/dl
Grado 4 (pericolosa per la vita)	< 6,5 g/dl	< 6,5 g/dl

Fisiopatologia dell'anemia oncologica



Cause dell'anemia nel pz neoplastico

FARMACI CITOTOSSICI

- ✓ Compromissione della funzionalità midollare (es. antracicline, ciclofosfamide)
- ✓ Nefrotossicità con ↓ della produzione di EPO (es. cisplatino)
- ✓ L'incidenza e la severità dipendono dal farmaco, dalla schedula, dalla dose e da precedente trattamento chemioradioterapico

ONCOLOGIA TREVIGLIO

Farmaci chemioterapici e anemia

		Anemia (% pazienti)	
Neoplasia	Farmaco/combinazione	Grado 1 / 2	Grado 3 / 4
NSCLC avanzato	Paclitaxel	23-100	5
	Docetaxel	73-85	2-10
	Paclitaxel/carboplatino	10-59	5-34
	Paclitaxel/cisplatino	45-60	5-23
Ca Ovaio avanzato	Carboplatino	66	0-26
	Cisplatino	8	2
	Paclitaxel/cisplatino	58	8
	Cisplatino/ciclofosfamide	32-97	2-29

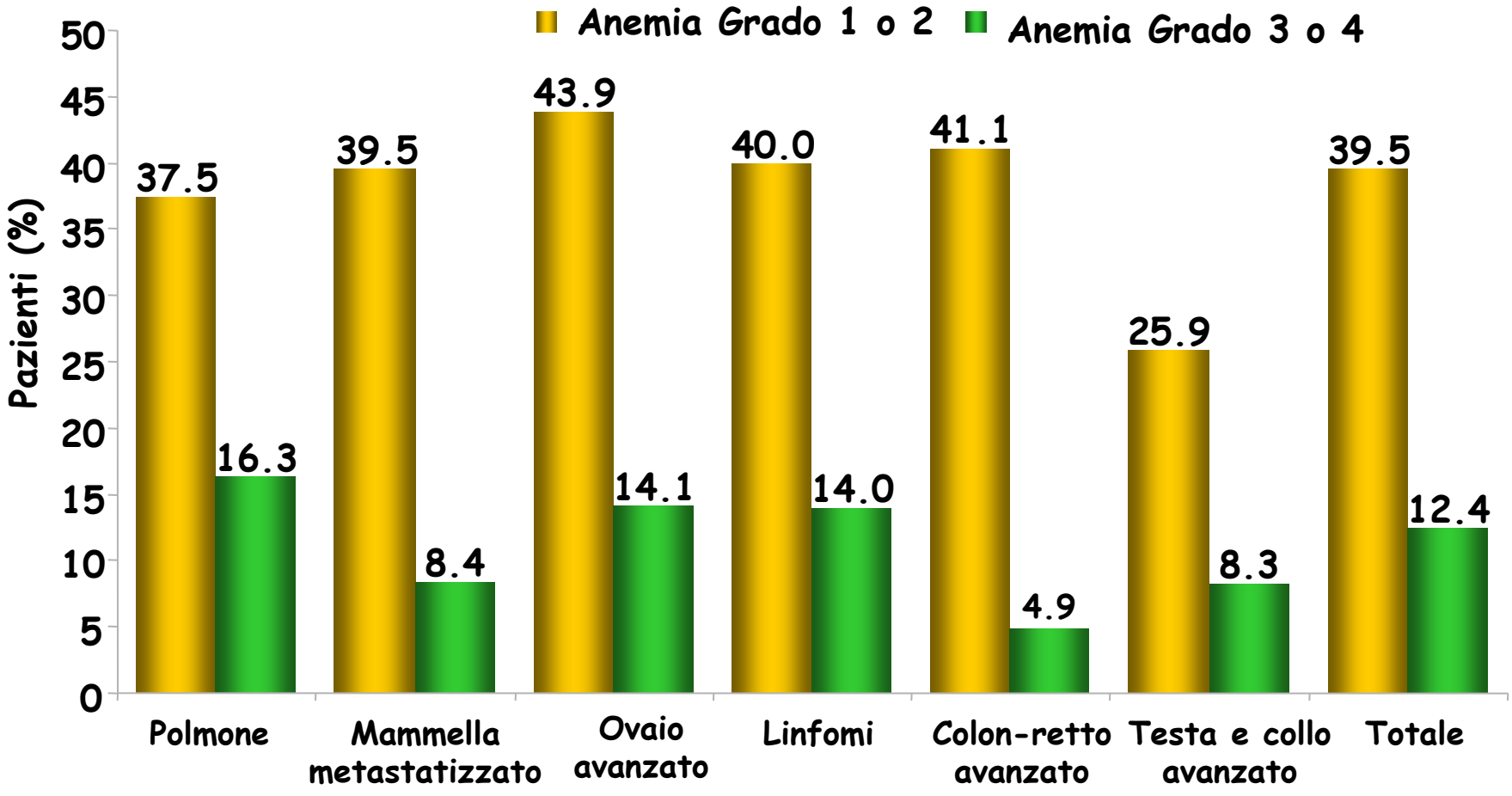
Groopman J. et al. J Natl Cancer Inst.1999;91:1616-34

Farmaci chemioterapici e anemia

		Anemia (% pazienti)	
Neoplasia	Farmaco/combinazione	Grado 1 / 2	Grado 3 / 4
Ca mammella metastatico	Paclitaxel	93	7
	Docetaxel	97	0-14
	CAF-M	27	1
NHL	CHOP	49	17-79
	MACOP-B	55	10
Ca colon retto avanzato	Irinotecan	60	8
	FUFA	6-53	2-5

Groopman JE. et al. J Natl Cancer Inst.1999;91:1616-34

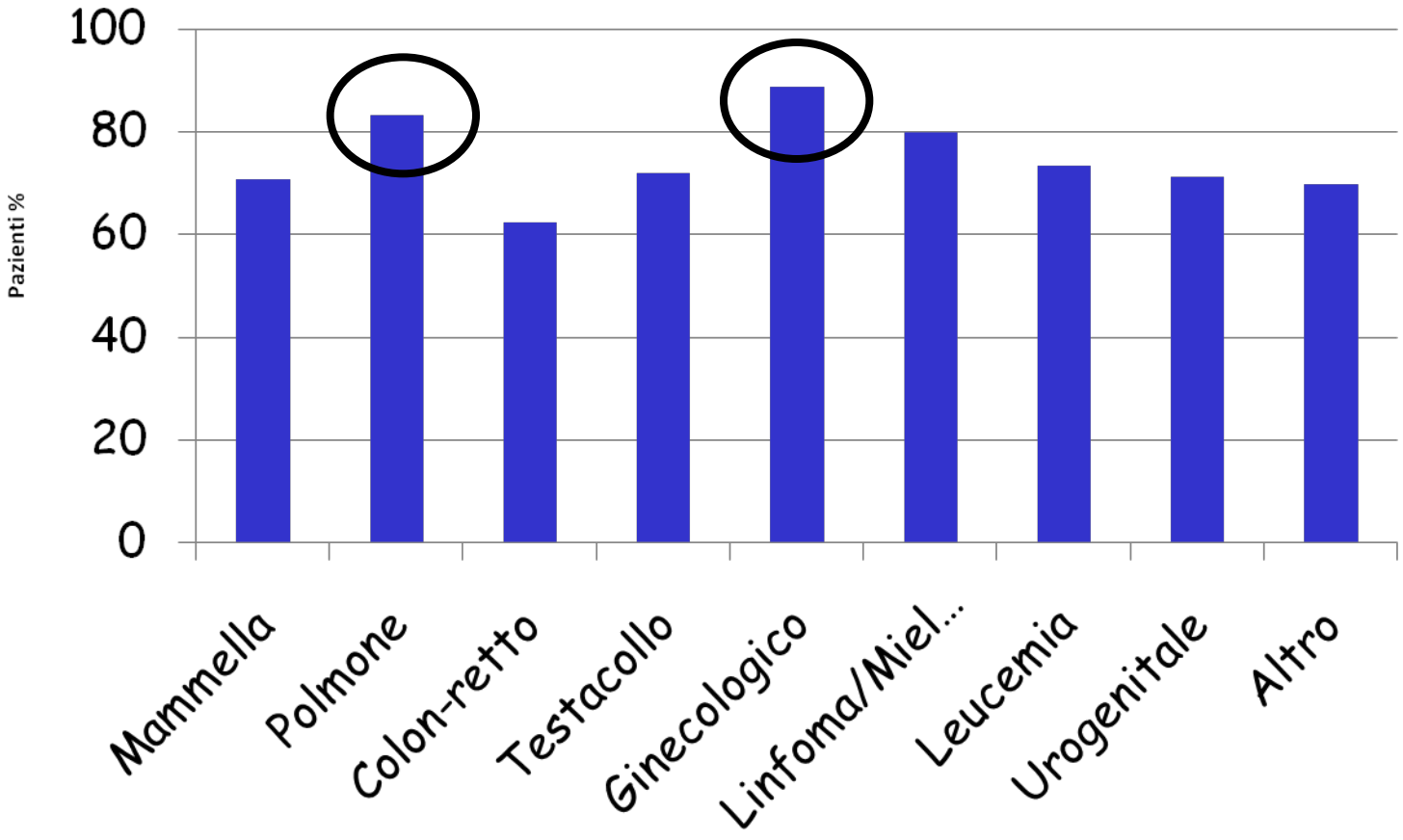
Incidenza anemia nei pazienti oncologici



Groopman JE, Itri LM. *J Natl Cancer Inst.* 1999;91:1616-1634.

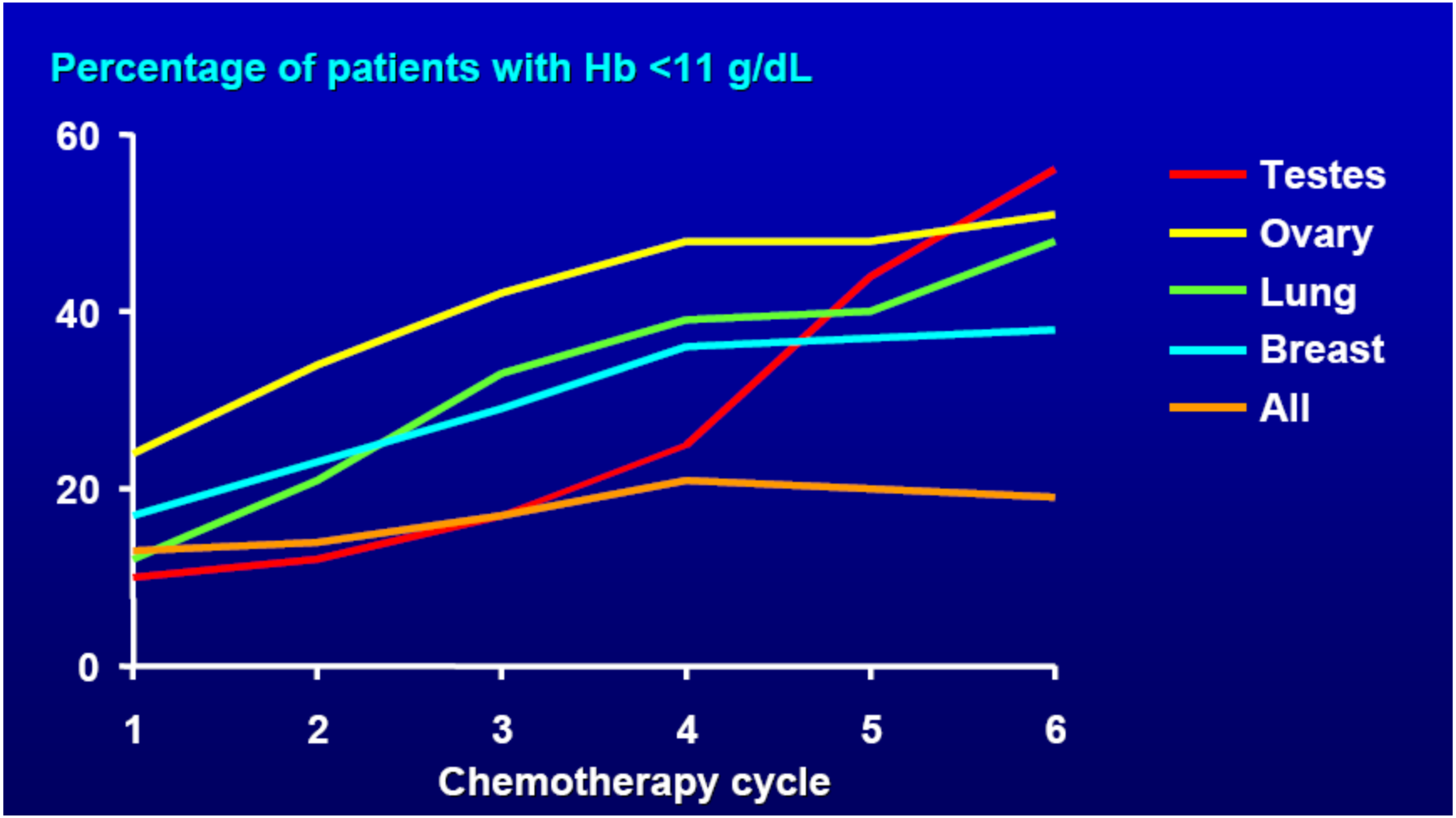
Oncologia Treviglio

Tipo di tumore



Oncologia Treviglio

Impatto della chemioterapia



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Cause dell'anemia nel pz neoplastico

FARMACI BIOLOGICI

The Oncologist®

Symptom Management and Supportive Care
return proof with your signature below
Approved by_____ Date_____

The Risk for Anemia With Targeted Therapies for Solid Tumors

SANDRO BARNI, MARY CABIDDU, PAOLO GUARNERI, VERONICA LONATI, FAUSTO PETRELLI

Oncology Department, Medical Oncology Unit, Azienda Ospedaliera, Treviglio, Italy

- ✓ 53 studi
- ✓ 24.310 pazienti valutabili per tossicità

Barni S.: The Oncologist 2012;12:000–000

ONCOLOGIA TREVIGLIO

Cause dell'anemia nel pz neoplastico

FARMACI BIOLOGICI

Incidenza globale	22.2 %
Anemia G1-G2	31.4 %
Anemia G3-G4	6.3 %

The Oncologist
The official journal of the Society for Translational Oncology

Barni S.: The Oncologist 2012;12:000-000

Oncologia Treviglio

Cause dell'anemia nel pz neoplastico

Erlotinb Trastuzumab Sutinib	RR 1.34 RR 1.19 RR 1.11	Rischio elevato
Bevacizumab	RR 0.73	Basso rischio p < 0.00001; absolute risk difference: -3%
Anti HER-2	RR 1.20	p. 0.0003
Anti EGFR	RR 1.24	p. 0.009
Anti-VEGF(R)	RR 0.82	p. 0.02
TKIs	RR 1.83	p. 0.005

Barni S.: The Oncologist 2012;12:000-000

ONCOLOGIA TREVIGLIO

Risk Factors for Becoming Anemic

2.585 Patients were not anemic at baseline, started on tumor treatment and followed for ≥ 2 cycles of chemo or had ≥ 2 observations during radiotherapy

Predictor Variable	Adjusted Odds Ratio	Wald * P-Values
Initial Hb: ≤ 12.9 (F) & ≤13.5 (M)	3.1	0.000
Lung/GYN vs. GI-colorectal	2.9	0.000
Platinum vs. Non-Platinum	2.3	0.000
All other Sites vs. GI-colorectal	2.4	0.000
Female vs. Male	1.9	0.000
Persistent/Recur vs. ND or IR	1.5	0.002
Age: ≥ 70 years vs. < 70 years	1.5	0.015
WHO PS 2/3/4 vs. 0/1	1.4	0.037
Highest BMI vs. Lowest BMI	0.6	0.000

* Statistic Software for Neural Network Analysis

Ludwig H. 2007

REVIEW

www.nature.com/clinicalpractice/onc

Cancer-related anemia and recombinant human erythropoietin—an updated overview

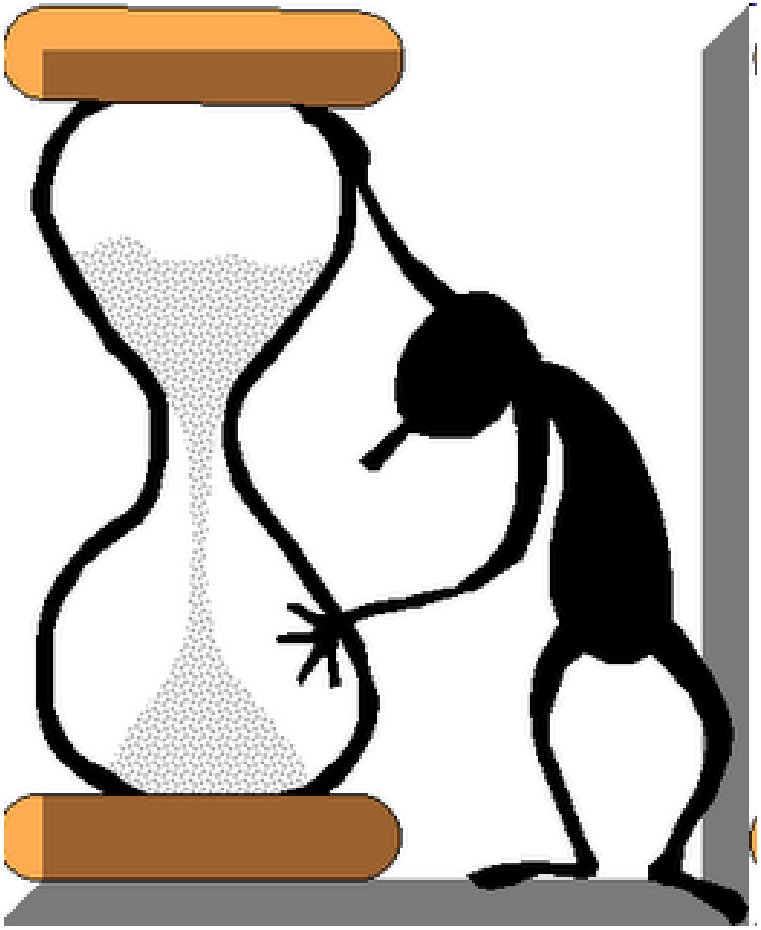
Julia Bohlius, Olaf Weingart, Sven Trelle and Andreas Engert*

- ✓ Fatigue
- ✓ Confusione mentale
- ✓ Deficit cognitivi
- ✓ Riduzione delle attività sociali e quotidiane
- ✓ Peggioramento della qualità di vita

Bohlius J. Nat Clin Pract Oncol. 2006;3(3):152-64.

Conseguenze dell'anemia da cancro

RIDUZIONE
DELLA
SOPRAVVIVENZA
?



Oncologia Treviglio

L'obiettivo della terapia con EPO

INCREMENTARE I LIVELLI DI Hb

RIDURRE LA NECESSITA' DI TRASFUSIONI

MIGLIORARE LA QUALITA' di VITA

ONCOLOGIA TREVIGLIO

Erythropoietin for anemia in cancer patients

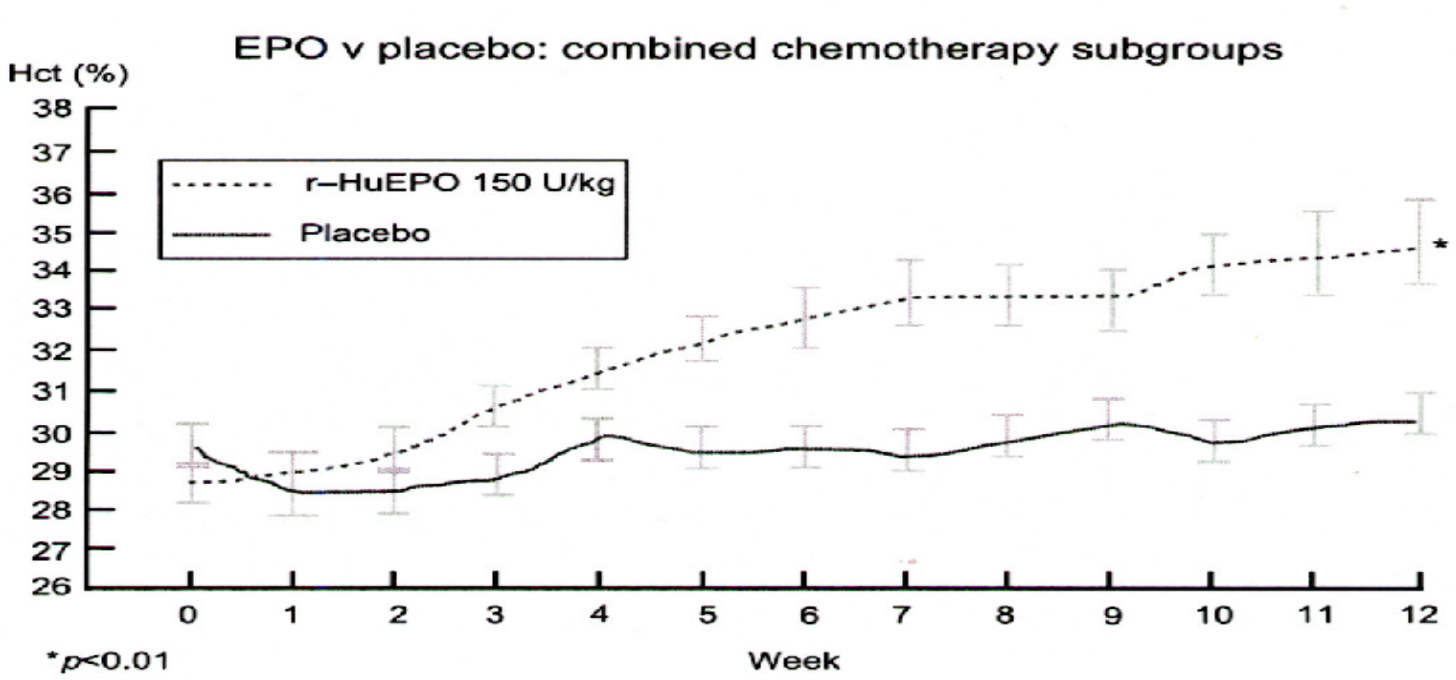


Figure 2. Mean Weekly Hct. EPO vs. placebo: combined chemotherapy subgroups.

FDA APPROVAL

ONCOLOGIA TREVIGLIO

Recombinant Human Erythropoietins and Cancer Patients: Update Meta-Analysis of 57 Studies including 9353 Patients

- ✓ Treatment with ESA
  - ➢ reduces transfusion requirement
  - ➢ improves hematopoietic response
  - ➢ provide clinically meaningful improvements in overall health in patients receiving chemotherapy

Bohlius J. Et al. J Natl Cancer Inst. 2006

ONCOLOGIA TREVIGLIO

I vantaggi

La qualità di vita

Study	Trial Type	Quality of Life Impact	Quality of Life Tool(s)
Glaspy 1997[1]	Open label	Yes	LASA
Demetri 1998[2]	Open label	Yes	LASA, FACT-An
Gabrilove 2001[3]	Open label	Yes	LASA, FACT-An
Littlewood 2001[4]	Randomized, placebo controlled	Yes	LASA, FACT-An, FACT-F, SF-36
Österborg 2002[5]	Randomized, placebo controlled	Yes	FACT-G, FACT-F, FACT-An
Boogaerts 2002[6]	Randomized	Yes	FACT-G, FACT-F, FACT-An, SF-36,
Vansteenkiste 2002[7]	Randomized, placebo controlled	Yes	FACT-F

1. Glaspy J, et al. J Clin Oncol. 1997;15:1218-1234. 2. Demetri GD, et al. J Clin Oncol. 1998;16:3412-3425. 3. Gabrilove JL, et al. J Clin Oncol. 2001;19:2875-2882. 4. Littlewood TJ, et al. J Clin Oncol. 2001;19:2865-2874. 5. Österborg A, et al. J Clin Oncol. 2002;20:2486-2494. 6. Boogaerts M, et al. Br J Med. 2002;88:988-995. 7. Vansteenkiste J, et al. J Natl Cancer Inst. 2002;94:1211-1220.

Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials

Julia Bohlius, Kurt Schmidlin, Corinne Brillant, Guido Schwarzer, Sven Trelle, Jerome Seidenfeld, Marcel Zwahlen, Michael Clarke, Olaf Weingart, Sabine Kluge, Margaret Piper, Dirk Rades, David P Steensma, Benjamin Djulbegovic, Martin F Fey, Isabelle Ray-Coquard, Mitchell Machtay, Volker Moebus, Gillian Thomas, Michael Untch, Martin Schumacher, Matthias Egger, Andreas Engert

Lancet 2009; 373: 1532–42

Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland (J Bohlius MD, K Schmidlin DMD, S Trelle MD, M Zwahlen PhD, Prof M Egger MD); Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany (C Brillant MSc, O Weingart MD, S Kluge MA, Prof A Engert MD); Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Freiburg, Germany (G Schwarzer PhD, Prof M Schumacher PhD); CTU Bern, Inselspital, Bern University Hospital, Bern, Switzerland (S Trelle, M Zwahlen); American Society of Clinical Oncology, Department of Cancer Policy and Clinical Affairs, Alexandria, VA, USA (J Seidenfeld PhD); UK Cochrane Centre, National Institute for Health Research, Oxford, UK

Summary

Background Erythropoiesis-stimulating agents reduce anaemia in patients with cancer and could improve their quality of life, but these drugs might increase mortality. We therefore did a meta-analysis of randomised controlled trials in which these drugs plus red blood cell transfusions were compared with transfusion alone for prophylaxis or treatment of anaemia in patients with cancer.

Methods Data for patients treated with epoetin alfa, epoetin beta, or darbepoetin alfa were obtained and analysed by independent statisticians using fixed-effects and random-effects meta-analysis. Analyses were by intention to treat. Primary endpoints were mortality during the active study period and overall survival during the longest available follow-up, irrespective of anticancer treatment, and in patients given chemotherapy. Tests for interactions were used to identify differences in effects of erythropoiesis-stimulating agents on mortality across prespecified subgroups.

Findings Data from a total of 13 933 patients with cancer in 53 trials were analysed. 1530 patients died during the active study period and 4993 overall. Erythropoiesis-stimulating agents increased mortality during the active study period (combined hazard ratio [cHR] 1·17, 95% CI 1·06–1·30) and worsened overall survival (1·06, 1·00–1·12), with little heterogeneity between trials (I^2 0%, p=0·87 for mortality during the active study period, and I^2 7·1%, p=0·33 for overall survival). 10 441 patients on chemotherapy were enrolled in 38 trials. The cHR for mortality during the active study period was 1·10 (0·98–1·24), and 1·04 (0·97–1·11) for overall survival. There was little evidence for a difference between trials of patients given different anticancer treatments (p for interaction=0·42).

Interpretation Treatment with erythropoiesis-stimulating agents in patients with cancer increased mortality during active study periods and worsened overall survival. The increased risk of death associated with treatment with these drugs should be balanced against their benefits.

Funding German Federal Ministry of Education and Research, Medical Faculty of University of Cologne, and Oncosuisse (Switzerland).

Bohlius J. Lancet 2009; 373: 1532–42

Interpretation:

Treatment with erythropoiesis-stimulating agents in patients with cancer increased mortality during active study periods and worsened overall survival.

The increased risk of death associated with treatment with these drugs should be balanced against their benefits.

Bohlius J. Lancet 2009; 373: 1532–42

British Journal of Cancer (2008) 99, 14–22

www.bjcancer.com

Clinical Studies

Effect of treatment with epoetin-β on survival, tumour progression and thromboembolic events in patients with cancer: an updated meta-analysis of 12 randomised controlled studies including 2301 patients

M Aapro*[,1], A Scherhag[2] and HU Burger[2]

[1]Institut Multidisciplinaire d'Oncologie, Clinique de Genolier, 1, route du Muids, Genolier CH-1272, Switzerland; [2]F Hoffmann-La Roche Ltd, Basel CH-4070, Switzerland

- ✓ **2.297 pz (epo = 1.244; controllo = 1.053)**
- ✓ **65% tumori solidi**

Aapro M. British Journal of Cancer (2008) 99, 14 – 22

- ✓ **Maggiore incidenza di eventi tromboembolici**
  - ➢ **7% vs 4%**
- ✓ **Mortalità per eventi tromboembolici simile**
  - ➢ **1% vs 1%**

CONCLUSIONS

The results of this meta-analysis including all prospective, randomised studies conducted with epoetin-β in cancer patients showed no evidence for a significantly negative effect of epoetin-β treatment on survival in patients with metastatic cancer. Furthermore, there was no negative effect of epoetin-β on tumour progression. The risk of TEEs was consistent with the increased TEEs risk observed within the ESA class in general, with a higher incidence of TEEs in patients with solid tumours. Predefined subgroup analyses in patients with an initiation Hb level corresponding to the current EORTC treatment guidelines (i.e., $Hb \leqslant 11\ g\,dl^{-1}$) confirm the safety of epoetin-β in the treatment of anaemia in patients with metastatic cancers receiving concurrent chemotherapy when used within its licensed indication.

Aapro M. British Journal of Cancer (2008) 99, 14 – 22

Venous Thromboembolism and Mortality Associated With Recombinant Erythropoietin and Darbepoetin Administration for the Treatment of Cancer-Associated Anemia

Charles L. Bennett, MD, PhD
Samuel M. Silver, MD, PhD
Benjamin Djulbegovic, MD, PhD
Athena T. Samaras, BA
C. Anthony Blau, MD
Kara J. Gleason, BS
Sara E. Barnato, MD
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D. Mark Courtney, MD
June M. McKoy, MD, MPH, JD
Beatrice J. Edwards, MD
Cara C. Tigue, BA
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Paul R. Yarnold, PhD
David A. Dorr, MD, MS
Timothy M. Kuzel, MD
Martin S. Tallman, MD
Steven M. Trifilio, RPh
Dennis P. West, PhD
Stephen Y. Lai, MD, PhD
Michael Henke, MD

Context The erythropoiesis-stimulating agents (ESAs) erythropoietin and darbepoetin are licensed to treat chemotherapy-associated anemia in patients with nonmyeloid malignancies. Although systematic overviews of trials have identified venous thromboembolism (VTE) risks, none have identified mortality risks with ESAs.

Objective To evaluate VTE and mortality rates associated with ESA administration for the treatment of anemia among patients with cancer.

Data Sources A published overview from the Cochrane Collaboration (search dates: January 1, 1985-April 1, 2005) and MEDLINE and EMBASE databases (key words: *clinical trial*, *erythropoietin*, *darbepoetin*, and *oncology*), the public Web site of the US Food and Drug Administration and ESA manufacturers, and safety advisories (search dates: April 1, 2005-January 17, 2008).

Study Selection Phase 3 trials comparing ESAs with placebo or standard of care for the treatment of anemia among patients with cancer.

Data Extraction Mortality rates, VTE rates, and 95% confidence intervals (CIs) were extracted by 3 reviewers from 51 clinical trials with 13 611 patients that included survival information and 38 clinical trials with 8172 patients that included information on VTE.

Data Synthesis Patients with cancer who received ESAs had increased VTE risks (334 VTE events among 4610 patients treated with ESA vs 173 VTE events among 3562 control patients; 7.5% vs 4.9%; relative risk, 1.57; 95% CI, 1.31-1.87) and increased mortality risks (hazard ratio, 1.10; 95% CI, 1.01-1.20).

Conclusions Erythropoiesis-stimulating agent administration to patients with cancer is associated with increased risks of VTE and mortality. Our findings, in conjunction with basic science studies on erythropoietin and erythropoietin receptors in solid cancers, raise concern about the safety of ESA administration to patients with cancer.

JAMA. 2008;299(8):914-924 www.jama.com

Bennett C. I. JAMA 2008

QUANDO
COME
QUANTO

ONCOLOGIA TREVIGLIO

Quando iniziarla

Recommendation	ASCO/ASH[1]	NCCN[2]	EORTC[3]
Initiate ESA therapy	Hb ≤ 10 g/dL (clinical decision if Hb > 10 - ≤ 12 g/dL)	Hb ≤ 11 g/dL	Hb 9-11 g/dL (clinical decision if Hb ≤ 11.9 g/dL)
Goal of treatment	Maintain Hb at or near 12 g/dL	Maintain between 10-12 g/dL	Target Hb should be 11-13 g/dL

1. Rizzo JD, et al. J Clin Oncol. 2008;26:132-149.
2. NCCN Clinical Practice Guidelines in Oncology.
3. Bokemeyer C, et al. Eur J Cancer. 2004;40:2201-2216.

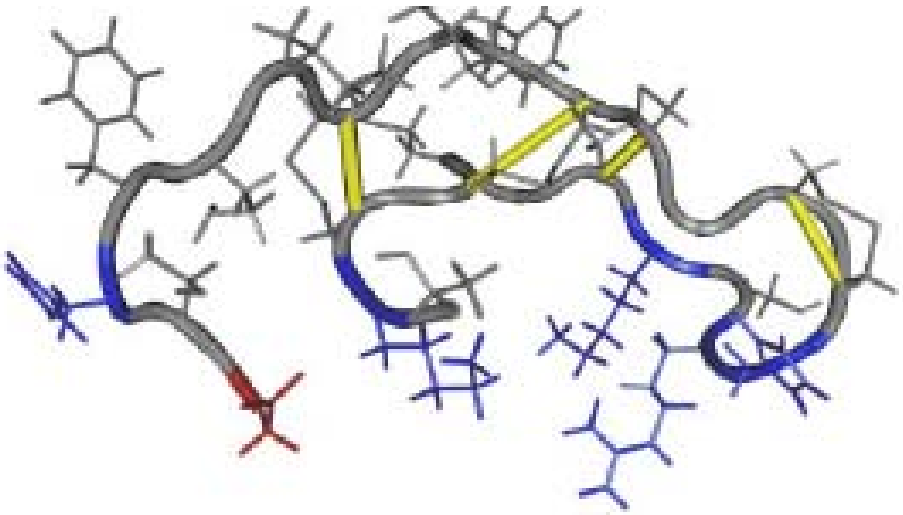
Quando iniziarla

Hb < 10 g/dL

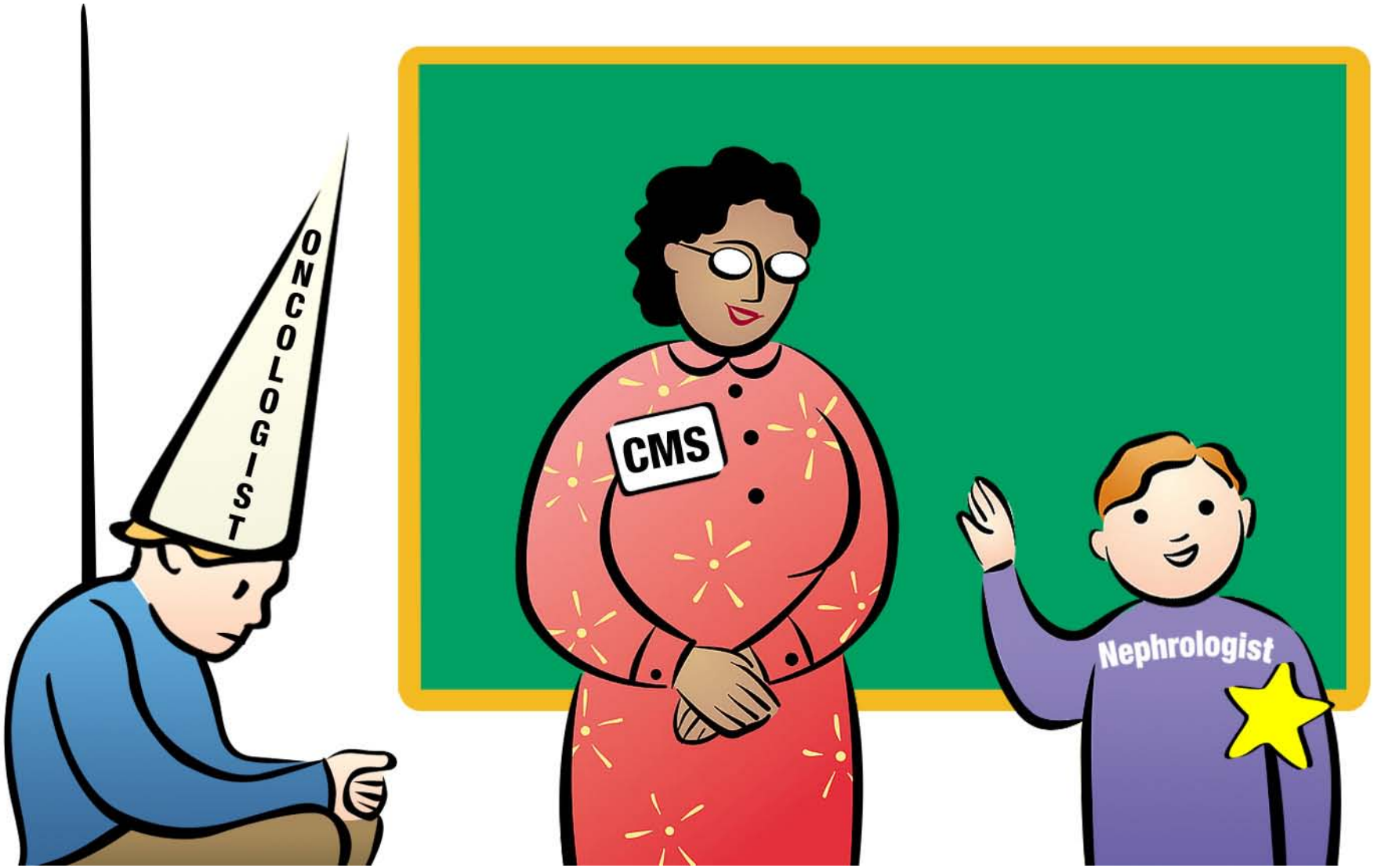
Oncologia Treviglio

Epcidina: struttura e funzione

- ✓ Epcidina è una proteina sintetizzata dal fegato in seguito a segnali infiammatori, ossigenazione (anemia, ipossia)
- ✓ Epcidina inibisce l'assorbimento intestinale di Fe e il rilascio di Fe da parte dei macrofagi
- ✓ Epcidina viene escreta con le urine , dove può essere misurata



Ganz, 2006



Courtesy P. Pedrazzoli

VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Multicenter, Controlled Trial Comparing the Efficacy and Safety of Darbepoetin Alfa Administered Every 3 Weeks With or Without Intravenous Iron in Patients With Chemotherapy-Induced Anemia

Laurent Bastit, An Vandebroek, Sevilay Altintas, Bernd Gaede, Tamás Pintér, Tamas S. Suto, Tony W. Mossman, Kay E. Smith, and Johan F. Vansteenkiste

VOLUME 26 · NUMBER 10 · APRIL 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial of Intravenous Iron Supplementation in Patients With Chemotherapy-Related Anemia Without Iron Deficiency Treated With Darbepoetin Alfa

Paolo Pedrazzoli, Antonio Farris, Salvatore Del Prete, Filomena Del Gaizo, Daris Ferrari, Clara Bianchessi, Giuseppe Colucci, Alberto Desogus, Teresa Gamucci, Alessandro Pappalardo, Giuseppe Fornarini, Paola Pozzi, Alessandra Fabi, Roberto Labianca, Francesco Di Costanzo, Simona Secondino, Enrico Crucitta, Federica Apolloni, Antonio Del Santo, and Salvatore Siena

LINEE GUIDA AIOM

Prima di iniziare il trattamento con agenti eritropoietici è necessario effettuare valutazione dello stato del ferro corporeo (Saturazione della transferrina, TSAT e ferritina) questo al fine di poter correggere, tramite adeguato supporto marziale per via endovenosa (EV), un eventuale carenza funzionale o assoluta di ferro nell'ambito di corretto impiego degli agenti eritropoietici.

Stato del ferro –linee guida

	AIOM 2009	ASCO/ASH	NCCN 2010
Parametri	TSAT, Ferritina	Sideremia, TSAT, Ferritina	Sideremia, TIBC, ferritina
supplementazione	Ferro ev	NR	Ferro ev

LINEE GUIDA AIOM 2009

La valutazione dello stato del ferro ha un'importanza cruciale per una corretta strategia terapeutica. Nei pazienti con carenza funzionale di ferro, la terapia con ESA è efficace solo se viene associata ad una terapia marziale per via EV . Nel paziente con carenza assoluta di ferro (TSAT <10 o ferritina al di sotto del range di normalità) è invece necessario anteporre una terapia marziale all'eventuale impiego degli ESA .

La terapia marziale

- ✓ La dose iniziale è di 125 mg di sodio ferrigluconato ev breve ogni 1-2 settimane sino a raggiungere la dose di 750-1000 mg in pz con sideremia normale o 2000 mg in pz con carenza funzionale

- ✓ L'utilizzo del ferro ev è controindicato in pz con sovraccarico marziale (TSAT > 50% e ferritina > 1000)

La terapia marziale

- ✓Il ferro somministrato per via orale è sostanzialmente inefficace nei pazienti con anemia associata a neoplasia

J Cancer Res Clin Oncol
DOI 10.1007/s00432-011-1072-3

REVIEW

Addition of iron to erythropoiesis-stimulating agents in cancer patients: a meta-analysis of randomized trials

Fausto Petrelli · Karen Borgonovo · Mary Cabiddu · Veronica Lonati · Sandro Barni

Conclusion Overall parenteral iron reduces the risk of transfusions by 23% and increases the chance of hematopoietic response by 29% when compared with ESAs alone. On the contrary, oral iron does not increase hematopoietic response nor transfusion rate. The significance of these results is that the proportion of non-responders to ESAs will have strongly improved and quality of life and cost ameliorated.

LINEE GUIDA AIOM

Il trattamento con ESA deve essere interrotto al raggiungimento dei 12 g/dl di Hb, quando è indicato interrompere il trattamento che poi andrà ripreso nel caso di una significativa riduzione dei livelli di Hb.

LINEE GUIDA AIOM

Va sottolineato che in tutti gli studi clinici in cui è stata evidenziata un aumentato rischio per il paziente,gli ESA sono stati somministrati al di fuori delle indicazioni approvate in relazione ai valori iniziali e finali di Hb e all'uso degli ESA in soggetti che non ricevevano chemioterapia.
L'autorità regolatoria italiana (AIFA) non ha pertanto modificato le indicazioni all'uso degli ESA nell'anemia associata a chemioterapia con Hb<10g/dL.

Recombinant Human Erythropoietins and Cancer Patients: Update Meta-Analysis of 57 Studies including 9353 Patients

(2006)

- ✓ Treatment with ESA
  - ➢ reduces transfusion requirement
  - ➢ improves hematopoietic response
  - ➢ provide clinically meaningful improvements in overall health in patients receiving chemotherapy
  - ➢ increases the risk of thrombotic events
- ✓ ESA should not be given if Hb>12g/dL
- ✓ When given according to guidelines ESA have no impact on survival

Bohlius J. Et al. J Natl Cancer Inst. 2006

ONCOLOGIA TREVIGLIO

RIFLESSIONI PERSONALI

- Anemia da CT
- Con HB < 10 g/dl
- Dopo studio metabolismo del ferro
- Stop a 12 g/dl
- Attenzione al tromboembolismo

To be continued

British Journal of Cancer (2012) 106, 1249 – 1258

www.bjcancer.com

Minireview

Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer

M Aapro[*,1], W Jelkmann[2], SN Constantinescu[3] and B Leyland-Jones[4]

[1]Institut Multidisciplinaire d' Oncologie, Clinique de Genolier, Route du Muids 3, PO Box 100, Genolier CH-1272, Switzerland; [2]Institute of Physiology, University of Lübeck, Ratzeburger Allee 160, Lübeck D-23538, Germany; [3]Ludwig Institute for Cancer Research and de Duve Institute, Université Catholique de Louvain, Avenue Hippocrate 74, UCL 75-4, Brussels B-1200, Belgium; [4]Winship Cancer Institute, Emory University, School of Medicine, 1365C Clifton Rd NE, Ste 4014, Atlanta, GA 30322, USA

ONCOLOGIA TREVIGLIO

INVITO

Sistema Sanitario Regione Lombardia

Azienda Ospedaliera Treviglio

Oncologia Medica Treviglio

SAVE THE DATE

19 OTTOBRE 2012

TREVIGLIO

Azienda Ospedaliera Treviglio - Caravaggio
SALA VERDE
P.le Ospedale, 1

il PROFUMO delle IDEE

DALLA SCIENZA ALL'ARTE MEDICA IN ONCOLOGIA

DIRETTORE DEL CORSO
Sandro Barni

Oncologia Treviglio