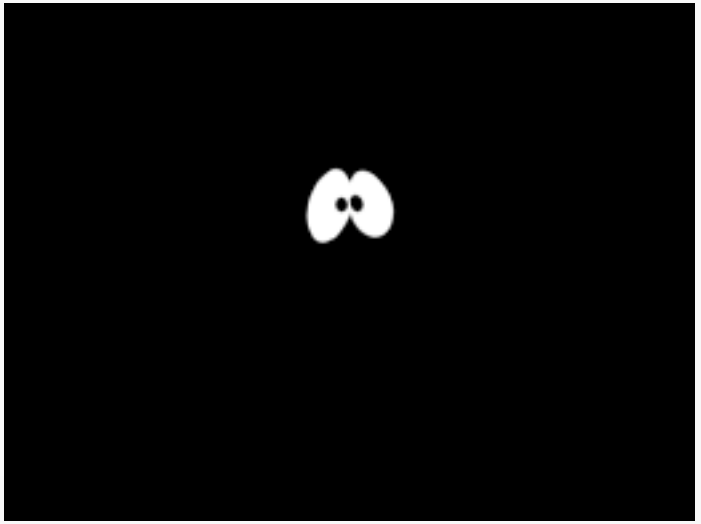
I° CONVEGNO REGIONALE SIFO "MEETING DI PRIMAVERA" –
"IL FARMACISTA CLINICO E I NUOVI MODELLI DI CURA"

Taormina, 11/12/13 maggio 2017

FATTORI DI CRESCITA:
Indicazioni e Formulazioni a Confronto.
La view dell'ematologo.



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ESAs

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Cancer- and Chemotherapy-Induced Anemia

NCCN Guidelines Index
Anemia Table of Contents
Discussion

COMPARISON OF RISKS AND GOALS OF ESA USE VERSUS RED BLOOD CELL TRANSFUSION[9]

If anemia is not due to absolute or functional iron deficiency, there are currently only two proven methods of improving Hb: ESAs and red blood cell transfusion. Listed below are risks and goals of each method.

	ESA in the Cancer Setting	Red Blood Cell Transfusion
Risks	• Increased thrombotic events • Possible decreased survival • Time to tumor progression shortened	• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury) • TACO • Virus transmission (eg, hepatitis, HIV) • Bacterial contamination • Iron overload • Increased thrombotic events • Possible decreased survival
Goals	• Transfusion avoidance • Gradual improvement in anemia-related symptoms	• Rapid increase of Hb and hematocrit levels • Rapid improvement in anemia-related symptoms

EUROPEAN JOURNAL OF CANCER 43 (2007) 258–270

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Review

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

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

From ESMO 2010 GUIDELINES

The European Medicines Agency (EMEA) labels the use of ESAs as follows:

In 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 or to prevent further decline in Hb [II, A].

In patients treated with curative intent, ESAs should be used with caution [D].

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

Table 1. Indications of ESA therapy according to NCCN, ESMA and ASH/ASCO guidelines. (REMS risk evaluation and mitigation strategy concerning the use of ESAs)

	NCCN	ESMO	ASH/ASCO
Indication			
Chemotherapy with curative intent	ESAs not recommended	ESAs are to be used with caution	ESAs not recommended though the term of curative intent is subject to debate
Palliative chemotherapy	Initiation of ESA therapy under REMS guidelines using the lowest dose necessary to avoid transfusions RBCT remain an option	ESAs may be considered	Initiation of ESA therapy with informed consent as to potential risks. RBCT remain an option
Cancer induced anaemia (untreated patient)	ESAs not recommended RBCT preferred	ESAs not indicated due to an increase in mortality especially if target hemoglobin 12-14g/dl	Not recommended
Initiation			
Hb level at initiation	<10g/dl or reduction of 2g/dl from baseline >10g/dl if symptomatic or high risk patient.	≤10g/dl to increase the Hb level to<12g/dl or to stabilize Hb level to avoid RBCT	<10g/dl in patients with Hb 10-12g/dl, ESAS are to be used according to circumstances and clinical judgement.
Unstable patient	RBCT recommended	Not assessed	RBCT recommended
Iron supplementation			
Type of supplementation	Parenteral iron only	Parenteral iron therapy yields a better increment than oral therapy	Not enough evidence to favour parenteral over oral iron supplementation
Initiation	If functional iron deficiency is present (ferritin<800ng/ml and transferrin saturation<20%)	If signs of functional iron deficiency are present (ferritin<100ng/ml and transferrin saturation<20%)	If signs of functional iron deficiency are present.

L. Plawny Belg J Hematol 2012;3:88-94

The European Medicines Agency (EMEA) labels use of ESAs

- In patients treated with chemotherapy and an Hb level < 10 g/dl, treatment with ESAs might be considered to increase Hb to < 12 g/dl or to prevent further decline in Hb [II, A].

- In patients not treated with chemotherapy, there is no indication for the use of ESAs and there might be an increased risk of death when ESAs are administered to a target Hb of 12–14 g/dl [I, A].

- In patients treated with curative intent, ESAs should be used with caution [D].

Key messages:

1) Cancer-or chemotherapy induced anaemia remains an exclusion diagnosis. Patients should be checked for other causes of anaemia. (blood loss denutrition, haemolysis, iron deficiency renal insufficiency or inflammation).

2) ESAs are recommended in cancer patients undergoing supportive chemotherapy. They are generally not recommended in patients not receiving chemotherapy (with the exception of myelodysplasia).

3) In patients receiving chemotherapy with a curative intent, most guidelines recommend against the use of ESAs.

4) Most studies indicating a negative effect of ESA therapy on overall survival had a Hb target>12g/dl. Recent data do not seem to support these suspicions.

5) The risk of venous thromboembolism is raised in patients receiving ESA treatment.

6) Parenteral iron should be given to patients receiving ESA especially if they display functional iron deficiency

L. Plawny Belg J Hematol 2012;3:88-94

Guidelines for Treatment of Anaemia in Patients with Cancer

"We confirm that QoL can be significantly improved in anaemic cancer patients following treatment of anaemia"

The two major goals of anaemia therapy are prevention of transfusions and improvement of QoL (grade A).

Cochrane meta-analysis on EPOs and QOL

Erythropoietin or darbepoetin for patients with cancer (Review)

Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J

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

THE COCHRANE COLLABORATION®

"unlike reports of original research, these articles represent the judgment of their authors, based on their evaluation of the literature. What studies they select to discuss and their analysis of them are necessarily subjective”

Kassirer JP, Angell M. Financial conflicts of interest in biomedical research. N Engl J Med. 1993 Aug 19;329(8):570-1

In patients with low-risk myelodysplastic syndromes ESAs can be used to improve anaemia.

- Patients with a higher average baseline serum EPO level (500 U/l) have a smaller Hb change and a lower rate of Hb response (27.3%) than groups with a lower baseline serum EPO level (34.9%).

- Treatment with ESAs should start at 450 IU/kg/week for at least 8–10 weeks.

- Predictors of response to ESAs include a normal karyotype, endogenous EPO levels <100–200 mU/ml and the refractory anaemia subtype.

rhG-CSF

Febrile Neutropenia

- Fever: Single oral temperature ≥38.3°C or persistent temperature ≥38.0 °C for >1 hour.

- Neutropenia: ANC <0.5, or ANC <1.0 and a predicted decline to <0.5 over next 48 hrs.

(ANC= absolute neutrophil count)

Predisposing Factors

- Malignancy
  - Type
  - Advanced/refractory
  - Obstructive
- Surgical risk
- Grade of neutropenia
- Disruption of mucosal barriers
- Corticosteroid use

Detailed History & Physical Exam Including

- Chemotherapy regimen & last dose given
- Presence of vascular devices
- Prophylactic antibiotic
- Steroid use
- Allergies
- Major comorbid illnesses
- Recent surgical procedures
- Recent infections or positive cultures
- Previous antibiotic-resistant organisms or bacteraemia
- Recent exposures

What is the Risk?

Incidence of Febrile Neutropenia	
Induction-remission for AML	70-90%
Elderly patients receiving CHOP	35-45%
Patients with NHL	10-20%
Mortality Estimates from Febrile Neutropenia	
Solid tumours	5%
Hematological malignancy	Up to 11%
Gram-positive bacteremia	5%
Gram-negative bacteremia	18%

Patient Related Risk Factors

a) Age: ≥ 65 (NHL)

b) Performance Status

c) Gender (female)

d) Comorbidities:

- Renal Disease, Cardiovascular Disease in NHL ---CHOP

e) Laboratory Abnormalities:

- ✓ Low lymphocytes or neutrophils count
- ✓ Low serum albumine
- ✓ Increased LDH, bilirubin, alkaline phosphatase

Treatment Related Risk Factors

1. Chemotherapy Regimen:

   Treatment containing:

   a) Anthracyclines,
   b) Taxanes,
   c) Alkylators
   d) Topoisomerase inhibitors
   e) Gemcitabine
   f) Vinorerlbine

2. Neutropenia Prophilaxis

Disease Related Risk Factors

1. Tumor type
2. Advanced Disease
3. Genetic Risk Factors
   a) Some Genotypes: *GSTP1 genotype in patients treated with fluorouracil + oxaliplatin (FOLFOX), MDM2 SNP309 and TP53 R72P genotypes were significantly associated with developing FN in patients treated with FEC*
   b) SNPs: evaluation of 26 single-nucleotide polymorphisms (SNPs) in patients with breast cancer treated with FEC; SNPs in the drug transporter gene *ABCC1/MRP1, as well as SNPs in the UGT2B7 and FGFR4 genes.*

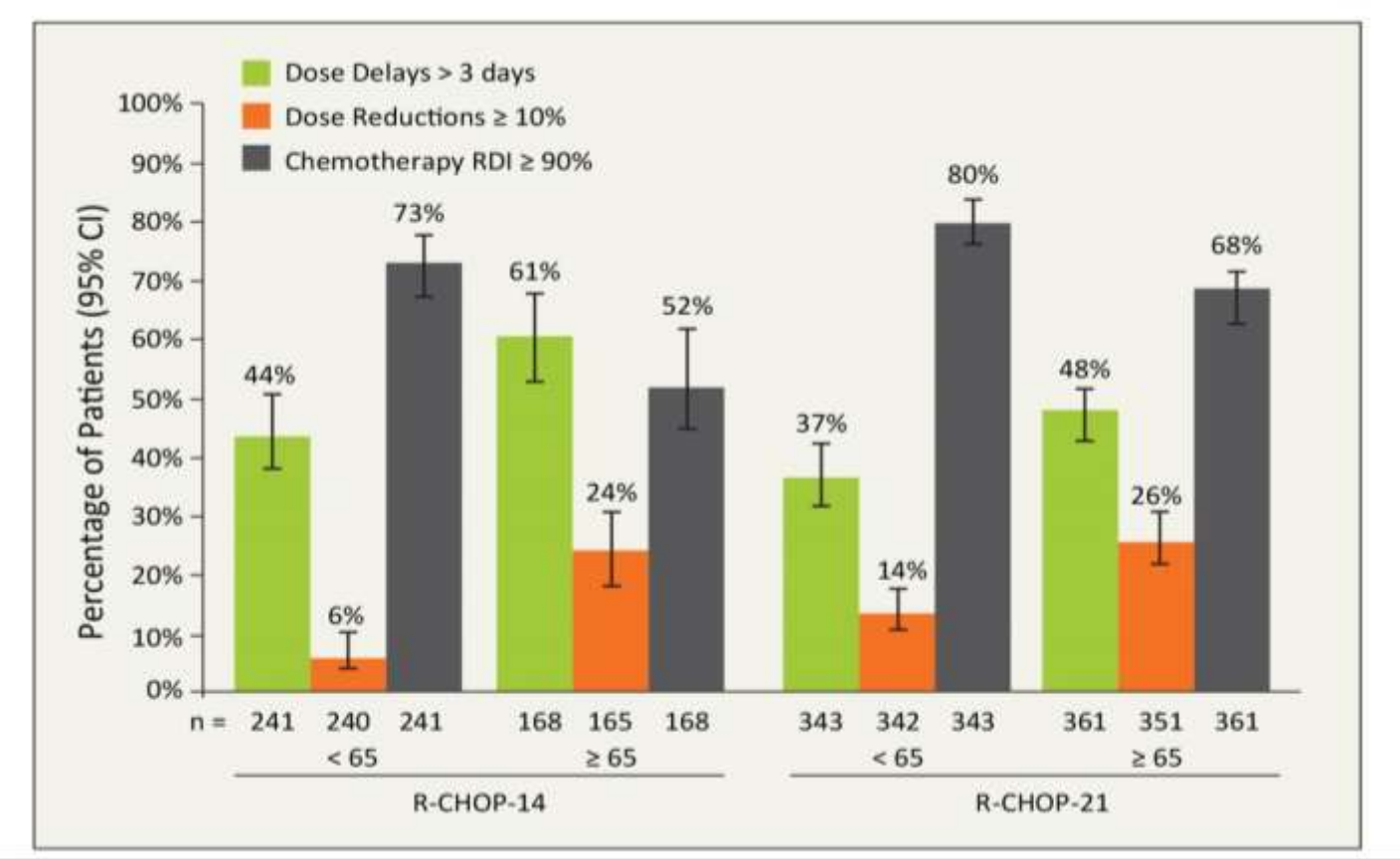
PATIENTS COMPLIANCE

- Diabetes (Insulin Treatment)
- Venous ThromboEmbolism (LMWH)
- Anemia (rhEpo)

DLBCL: Neutropenia Contributes to Dose Delays and Reductions

- Patients with DLBCL treated with R-CHOP-21 (n = 704) or R-CHOP-14 (n = 409)
- Dose delays were due to neutropenia (12%–16%), other nonhaematologic AEs (19%–26%), and other AEs (25%–26%)
- Dose reductions were primarily due to neurologic toxicity (30%–53%)

Dose Delays and Dose Reductions and Achievement of Chemotherapy RDI >90%

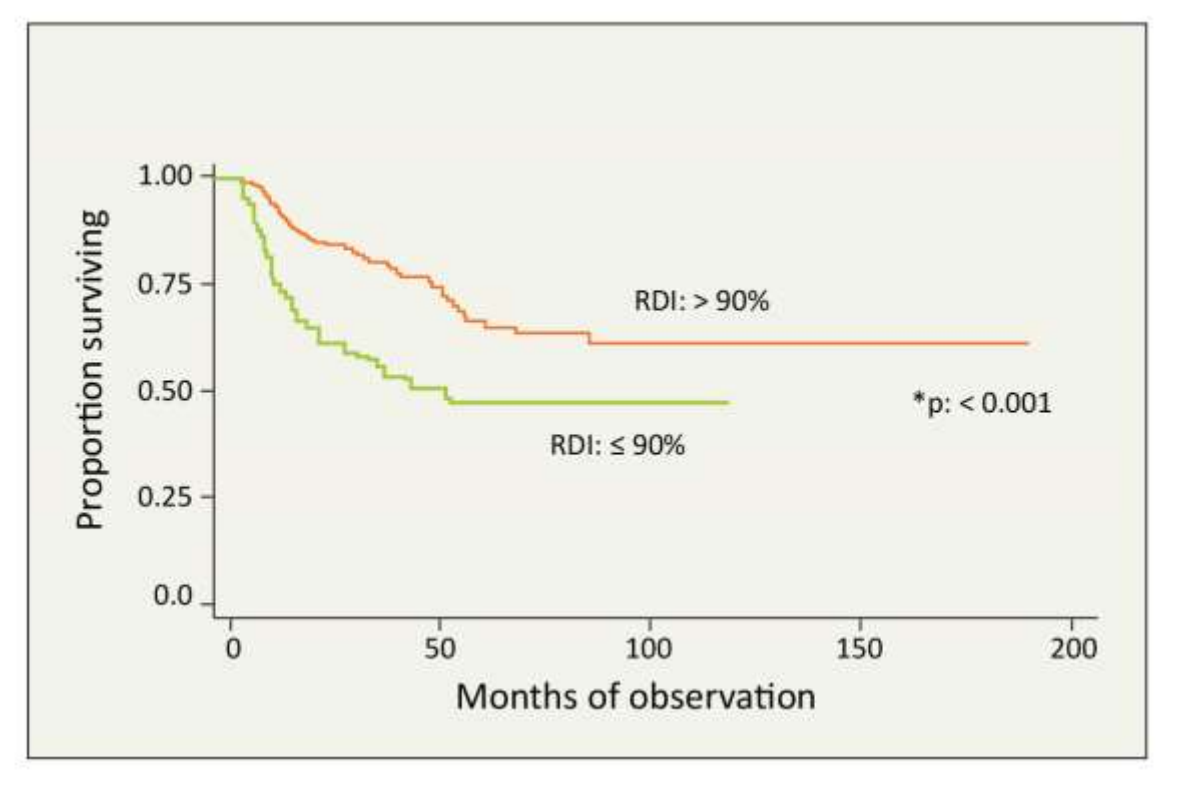


Lugtenburg P, et al. *Clin Lymphoma Myeloma Leuk.* 2012;12:297-305.

NHL: Chemotherapy Dose Reductions Negatively Affect Survival

Combined Belgian and UK data (n = 289)

- Lymphoma patients receiving CHOP-21



Delivering full chemotherapy dose intensity remains an important goal in NHL patients who receive CHOP-21 chemotherapy

Lugtenburg P, et al. *Clin Lymphoma Myeloma Leuk.* 2012;12:297-305.

Table III. Costs and reimbursement associated with hospitalized cancer patients with neutropenic complications.

	Neutropenia[a,b] (n=3,766)	Neutropenia plus infection or fever[b,c] (n=1,767)	Neutropenia without infection or fever[b,c] (n=1,999)	Neutropenia plus infection[b,d] (n=1,147)
Hospitalization costs, mean (95% CI) US$	18,042 (16,997-19,087)	22,839 (21,006-24,672)	13,801 (12,716-14,887)	27,587 (24,927-30,247)
Hospital reimbursements, mean (95% CI) US$	18,052 (16,769-19,335)	23,191 (20,936-25,446)	13,367 (12,067-14,667	26,321 (23,165-29,478)
Difference (loss) (95% CI), US$	11 (-1,051 to 1,073)	353 (-1,632 to 2,338)	435 (-1,356 to 487)	1,266 (-4,110 to 1,578)
Proportion of hospitalization costs reimbursed (%)	100.1	101.5	96.9	95.4

[a]Excludes patients who died within 1 day of admission. [b]Includes patients with neutropenia plus infection or fever, patients with neutropenia plus infection and patients with neutropenia without infection or without fever. [c]These patients are a subset of the patients with neutropenia. [d]These patients are a subset of the patients with neutropenia plus infection or fever.

Schilling MB et al. Exper Ther Med, 2011 859-866

ESA Treatment Recommendations

Chemotherapy-induced anaemia

Doses of ESAs according to ESMO and/or based on EMA label				
	Epoetin alpha zeta*[1]	**Epoetin beta[1]**	**Darbepoetin alpha[1]**	**Epoetin theta[2]**
Initial dose	150 IU/kg sc tiw or 450 IU/kg qw	30,000 IU sc qw	2.25 mg/kg sc qw 500 mg (6.75 mg/kg) sc q3w	20,000 IU sc qw
Dose increase	300 IU/kg sc tiw	60,000 IU sc qw	Not recommended	If Hb rise <1g/dl/4weeks: 40,000 IU qw If Hb rise insufficient after 4weeks: 60,000 IU qw
Dose reduction	If result achieved: 25-50% If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%	If result achieved: 25-50% If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%	If result achieved: 25-50% If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%	If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%
Dose withholding	If Hb>13 g/dl until 12g/dl	If Hb>13 g/dl until 12g/dl	If Hb>13 g/dl until 12g/dl	If Hb>13 g/dl until 12g/dl

sc, subcutaneous; tiw, thrice weekly; qw, once weekly; q3w, once every 3 weeks.

1. Schrijvers D, et al. *Ann Oncol.* 2010;21 Suppl 5:v244-v247; *2. European Medicines Agency. Eporatio – Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001033/WC500043300.pdf Accessed 09 February 2015

Grazie per l’attenzione