UNIVERSITA' DEGLI STUDI DI BRESCIA
Facoltà di Medicina e Chirurgia

"THE RIGHT TIMING FOR THE USE OF GROWTH FACTORS IN THE INTEGRATED TREATMENT OF HODGKIN AND NON HODGKIN LYMPHOMA"

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GROWTH FACTORS IN SUPPORTIVE THERAPY:WHICH?WHEN?

DIFFERENT GUIDELINES:

ASCO, NCCN, EORTC, AIOM

WHAT'S HAPPENED IN LAST DECADES?

- Prognosis improvement in HL and NHL (dose-intensity, dose-density)
- Increased Hematologic Toxicity
- Increased Risk of Febrile Neutropenia (FN)

(Aapro MS Eur J Cancer 2006, Crawford J Cancer 2004)

WHICH GROWTH FACTORS?

- ESAs (erithropoiesis-stimulating agents)
- GM-CSF,G-CSF (Granulocyte-macrophage colony-stimulating factors)
- KGF (keratinocyte growth factor)

(Stiff PJ JCO 2006)

CHEMOTHERAPY- INDUCED TOXICITY 1.

SCHEME	NEUTROPENIA grade 3-4(%)	FEBRILE NEUTROPENIA (%)	INFECTIONS grade 3-4(%)
Hodgkin lymphoma			
ABVD	25-66	3	1
BEACOPP-21 standard	60	20	10
BEACOPP-21escalated	90	25	15
BEACOPP-14	70	21	15
Stanford V	29		0
Non Hodgkin lymphoma			
CHOP 21	42-89	5-10	3-20
R-CHOP 21	55-78	2-33	5-17
R-CHOP 14+G-CSF	53	16	18
ACVBP	78	75	41
CODOX-M/IVAC	100	45	
HyperCVAD	100	30	
Salvage Therapy			
HAP		30	
DHAP	53	48	31
R-ICE	47-77	8-14	0-70
EPOCH+G-CSF	50	17	
Dexa BEAM	100	54	10

(Brusamolino E, Ferrara F Suppl.Tumori 2010)

CHEMOTHERAPY- INDUCED TOXICITY 2.

Position Paper

EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours

M.S. Aapro[a,*,m], D.A. Cameron[b,n], R. Pettengell[c,o], J. Bohlius[d,p], J. Crawford[e,q], M. Ellis[f,r], N. Kearney[g,s], G.H. Lyman[h,t], V.C. Tjan-Heijnen[i,u], J. Walewski[j,v], D.C. Weber[k,w], C. Zielinski[l,x], European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party

Table 5 – Intensive chemotherapy regimens supported by G-CSF

Malignancy	Chemotherapy regimen and level of evidence		Reference
Dose dense regimens (increased frequency)[a]			
Breast cancer	FEC	I	Capotorto et al. [133]
	Epirubicin/cyclophosphamide		Therasse et al. [63]
	Doxorubicin → paclitaxel → cyclophosphamide		Citron et al. [62]
	Doxorubicin/cyclophosphamide → paclitaxel		Citron et al. [62]
	MMM	III	Capotorto et al. [133]
NHL	R-CHOP	II	Pfreundschuh et al. [4]
			Sonneveld et al. [40]
SCLC	ACE	II	Ardizzoni et al. [77]; Thatcher et al. [38]
	CAV → PE (alternating weekly)		Masutani et al. [82]
	VICE (≥ Q2W, not fixed)		Woll et al. [81]
	CODE (QW)		Furuse et al. [84]
	Cisplatin/epirubicin/paclitaxel		Frasci et al. [134]
NSCLC	Cisplatin/vindesine/mitomycin C (PVM)	II	Masutani et al. [135]
Urothelial cancer	MVAC	II	Sternberg et al. [114]
Dose intense regimens (increased dose)			
HD	BEACOPP	II	Diehl et al. [136]
Ovarian cancer	Paclitaxel	II	Omura et al. [106]
SCLC	ACE	II	Ardizzoni et al. [77]
Dose modified regimens (withdrawal of one drug and increase in the dose of the remainder)			
Breast cancer	Epirubicin/cyclophosphamide with withdrawal of 5-FU	I	Therasse et al. [63]
	Cyclophosphamide with high-dose mitoxantrone and withdrawal of doxorubicin	III	Fumoleau et al. [66]

5-FU = 5-flourouracil; ACE, doxorubicin/cyclophosphamide/etoposide; BEACOPP, bleomycin/etoposide/doxorubicin/cyclophosphamide/vincristine/procarbazin e/prednisone; CAV → PE, cyclophosphamide/ doxorubicin/vincristine followed by cisplatin/etoposide; CODE, cisplatin/vincristine/doxorubicin/etoposide; FEC, cyclophosphamide/epirubicin/fluorouracil; HD, Hodgkin's disease; MMM, mitoxantrone/methotrexate/mitomycin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; PVM, cisplatin/vindesine/mitomycin C; Q2W, once every 2 weeks; QW, once per week; SCLC, small cell lung cancer; VICE, vincristine/ifosfamide/carboplatin/etoposide.

a The dose dense regimens were given every 2 weeks, unless otherwise specified.

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OTHER FN RISK FACTORS NOT CT RELATED?

- Perspective clinical models in lymphoma patients not receiving CSF prophylaxis: high levels LDH, TNF, bone marrow involvement as FN risk factors

(Voog E et al 2000 - JCO, 18, 325-331)

OTHER FN RISK FACTORS NOT CT RELATED?

bjh research paper *(Pettengell R et al 144, 677-685 Dec 2008)*

Multivariate analysis of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma: data from the INC-EU Prospective Observational European Neutropenia Study

- Factors associated with cycle 1 FN: older age, increasing planned cyclophosphamide dose, increasing planned etoposide dose, an history of recent infection, low baseline albumin <35g/L

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REVIEW ARTICLE

Impact of Primary Prophylaxis With Granulocyte Colony-Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: A Systematic Review

Nicole M. Kuderer, David C. Dale, Jeffrey Crawford, and Gary H. Lyman

Table 1. Summary of Randomized Controlled Trials of Primary Prophylactic G-CSF in Adult Patients Receiving Conventional Chemotherapy

Study	Year of Publication	No. of Patients	Tumor Category	Age Range (years)	G-CSF Type and Dosing*	Start Day†	Cycle Day‡	Length of G-CSF Therapy (days)	Stop Criteria§	Additional Treatments¶	Study Design Parameters
Zinzani et al[18]	1997	149	Lymphoma	60-82	Filgrastim 5 μg/kg QD	2	3	5	After 5 days	Secondary G-CSF: prophylaxis in controls: unknown Prophylactic antibiotics: yes	Placebo: no Blinding description: no Random assignment description: no Withdrawal description: yes
Gisselbrecht[19]	1997	162	Lymphoma	15-55	Lenograstim 5 μg/kg QD	1	6	8	After 8 days	Secondary G-CSF: prophylaxis in controls: unknown Prophylactic antibiotics: no	Placebo: yes Blinding description: no Random assignment description: no Withdrawal description: yes
Fossa et al[20]	1998	259	Solid tumor	15-65	Filgrastim 5 μg/kg QD	1	3 or 5	7 or 14	After 7 days or 14 days, depending on chemotherapy	Secondary G-CSF: prophylaxis in controls: unknown Prophylactic antibiotics: unknown	Placebo: no Blinding description: no Random assignment description: no Withdrawal description: no
Gatzemeier et al[43]	2000	280	Solid tumor	39-75	Lenograstim 150 μg/m^2 QD	1	4	10	After 10 days	Secondary G-CSF: prophylaxis in controls: unknown Prophylactic antibiotics: unknown	Placebo: no Blinding description: no Random assignment description: no Withdrawal description: yes
Doorduijn et al[46]	2003	389	Lymphoma	65-90	Filgrastim 300 μg QD	1	2	10	After 10 days	Secondary G-CSF: prophylaxis in controls: unknown Prophylactic antibiotics: no	Placebo: no Blinding description: no Random assignment description: no Withdrawal description: yes
Ösby et al[47] (CHOP)	2003	205	Lymphoma	60-86	Filgrastim 5 μg/kg QD	1	2	10-14	After 10 days if ANC > 10 × 10^9/L; otherwise, after 14 days	Secondary G-CSF: prophylaxis in controls: no Prophylactic antibiotics: no	Placebo: no Blinding description: no Random assignment description: yes Withdrawal description: no
Osby et al[47] (CNOP)	2003	203	Lymphoma	60-86	Filgrastim 5 μg/kg QD	1	2	10-14	After 10 days if ANC > 10 × 10^9/L; otherwise, after 14 days	Secondary G-CSF: prophylaxis in controls: no Prophylactic antibiotics: no	Placebo: no Blinding description: no Random assignment description: yes Withdrawal description: no

(continued on next page)

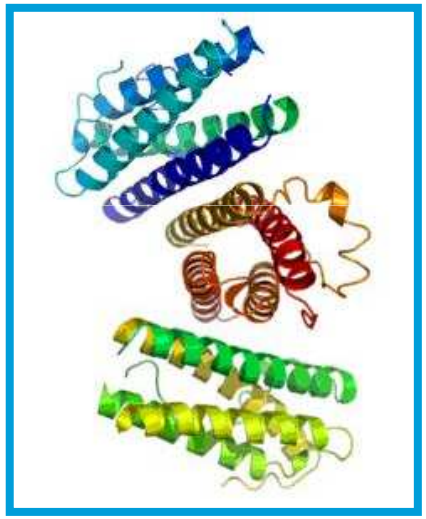
WHICH CSF CAN WE USE IN CLINICAL PRACTICE TO SUPPORT HL AND NHL PATIENTS ?

- **FILGRASTIM**
- **LENOGRASTIM (glycosylated)**

T1/2 3-4 hours

- **PEGFILGRASTIM (pegylated)**

T1/2 33 hours



WHEN CAN WE USE G-CSF IN HL AND NHL?

1. Chemotherapy

- **HL: ABVD** ⇨ no G-CSF prophylaxis

  BEACOPP escalated ⇨ primary prophylaxis

  ⇨ support intensity-dose

- **NHL: CHOP 21, R-CHOP21** ⇨ always primary prophylaxis in elderly patients

  ⇨ evaluation for comorbidity and additional risk

- **SALVAGE THERAPY: ESHAP, DHAP, R-ICE**

  ⇨ primary prophylaxis

(Brusamolino E, Ferrara F Suppl.Tumori 2010)

WHEN CAN WE USE G-CSF IN HL AND NHL?
2. HSC Autologous transplantation

- **<u>Mobilization PBSC</u>** ⇨ Lenograstim it's better?

  (Ria R et al 2008)

- **<u>Post transplantation</u>**: ⇨ prophylaxis of FN

  ⇨ decrease neutropenia duration, infections risk, antibiotic therapy and hospitalization duration.

(Brusamolino E, Ferrara F Suppl.Tumori 2010)

WHEN CAN WE USE G-CSF IN HL AND NHL: 3. PRE Radiotherapy??

- **RT POST CT:** "Patients with neutropenia, large field of irradiation"

(AIOM guidelines 2009 – Smith JCO 2006)

WHEN CAN WE USE G-CSF IN HL AND NHL?
4. During Radiotherapy?

- "Use of filgrastim, in RT to reduce dropouts for radiogenic leukopenia" *(Gava Radiol Med 1998)*

⇨ *Treviso group 1998*:

31 patients with WBC <2500-3000/µL (13 HD, 1 NHD and others tumours) during RT

PTV average volume: 5613 cm^3, range 1292- 13357 cm^3

" ….Filgrastim safe and useful to avoid delay in RT ….Better higher dosage in patients with big target and persistent leukopenia during previous CT"

…..During Radiotherapy??.....

- **"Use of pegfilgrastim in multimodal treatment in radiotherapy"**

  (Bartzsch O et al Strahlenther Onkol 1998)

  ⇨ *Munich Group:* 50 patients (12 HD and NHD and others tumours)

  ⇨ ***large field RT***

" … Give on time G-CSF when we expecte a decrease of leucocytes lower then 1000/mm³….around 1600/mm³"

…..During Radiotherapy??.....

- **“ Comparison of two strategies for the treatment of radiogenic leukopenia using G-CSF”**

  (A. Adamietz et al Int J Rad Onc Biol Phys 1996)

⇨ *Frankfurt Group:* 39 patients (15 NHD and 12 HD and others)

⇨ ***Mantle field and Inverted Y-field***

“….serial application of G-CSF vs intermitted injection as required.. …no statistical difference in the number of leukopenia-induced RT interruption…. “

…..During Radiotherapy??.....

- **" G-CSF during large field radiotherapy reduces bone marrow recovery capacity"**

(Pape H et al Strahlenther Onkol 2006)

⇨ *Duesseldorf Group:* 10 patients (1 HD and 7 NHD and others tumours)

⇨ ***large field RT alone vs RT + G-CSF***

"…peripheral leukocyte count at baseline levels"

⇨ ***These recommendations should be kept for a small part of patients!***

G-CSF TIMING 1.

- **Prophylaxis:**

-Filgrastim and Lenograstim 24-72 hours after CT cycle.

-After nadir, until neutrophil count is 1000/mm3

(Smith TJ et al JCO 2006-Aapro EJC 2006)

- **Begin of G-CSF 4 days after** CT cycle or after onset of neutropenia it's not effective and it doesn't decrease neutropenia complication.*(Kuderer JCO 2007-Repetto L EJC 2003)*

G-CSF TIMING 2.

- **<u>Don't give G-CSF 48 hours before CT cycle.</u>**

(*Smith TJ et al JCO BolwellBMT 1998)*

- **<u>Don't stop –G-CSF</u>:** after early increasing of neutrophil count (physiological process!)

(*Repetto L EJC 2003)*

- **<u>After autologous stem cell transplantation</u>: open discussion. (+1day vs +7, 0 day vs+3 vs +5)**

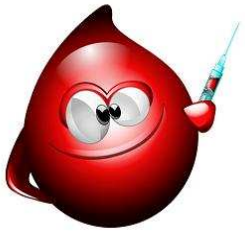
(*Bence-Bruckler I MBT 2005- Djulbegovic B, JCO 2005)*

WHICH ESAs CAN WE USE IN CLINICAL PRACTICE TO SUPPORT HL AND NHL PATIENTS ?

- **EPOETIN ALFA** } T1/2 24 hours sc
- **EPOETIN BETA** } T1/2 13-28 hours sc
- **DARBEPOETIN ALFA** } T1/2 24-144 hours sc

ESAs

- **EORTC guidelines for the use of ESAs in anaemic patients: update** *(EJC 2007)*



- **QUESTIONS:**

Table 2 – Questions addressed by the guidelines

In anaemic patients with cancer

1. Is 9–11 g/dL the standard range for initiation of therapy with erythropoietic proteins?
2. Is the target Hb concentration 12–13 g/dL?
3. Does treatment with erythropoietic proteins have a positive impact on Hb levels?
4. Does increasing the dose of erythropoietic proteins in non-responders produce a subsequent response?
5. Does treatment with erythropoietic proteins decrease RBC transfusion requirements?
6. Does treatment with erythropoietic proteins lead to QoL improvements?
7. Does treatment with erythropoietic proteins improve survival?
8. Is less frequent dosing of erythropoietic proteins possible (i.e. less than three times per week)?
9. Do higher initial doses of erythropoietic proteins produce higher haematological responses (i.e. higher than current standard practice of 30,000–40,000 IU/week)?
10. Do baseline patient parameters impact on response to erythropoietic proteins?
11. Can erythropoietic proteins be used prophylactically to prevent anaemia?
12. Can a fixed, rather than a weight-based, dose of erythropoietic protein be used?
13. Does PRCA occur following treatment with erythropoietic proteins?
14. Are the risks for thromboembolic events and hypertension increased in patients receiving erythropoietic proteins?
15. Does iron supplementation increase the response rate to erythropoietic proteins?
    a) Oral supplementation
    b) Intravenous supplementation

Abbreviations: Hb, haemoglobin; RBC, red blood cell; QoL, quality of life; PRCA, pure red cell aplasia.

TIMING
IN CT AND RT INDUCED ANAEMIA

- **PATIENTS UNDERGOING CT AND OR/RT**:
start with ESAs at 9-11g/dL based on anaemia-related symptoms (grade A).

- **ASYMPTOMATIC PATIENTS** with a Hb ≤11.9g/dL to prevent a further decreasing in Hb, according to individual factors (type/intensity CT, baseline Hb) and duration, type of further treatment (grade B).

(Bokemeyer C et al, EJC 2007)

TIMING IN CT INDUCED ANAEMIA

- **DON'T USE ESAs:** for prophylaxis with normal Hb values
- **Hb TARGET:** 12-13g/dL
- -QW Epoetin alfa 40000 IU (grade B)

-QW Epoetin beta 30000 IU for hematological diseases (grade B)

-QW or Q3W (grade A)

- **DON'T USE ESAs:** for patients undergoing autologous blood stem cell transplantation (grade B)

(Bokemeyer C et al, EJC 2007)

RADIOTHERAPY INDUCED ANAEMIA?

- *Rades D et al Cancer 2005*
- *Antonadou D Eur J Cancer Suppl 2003*
- *Antonadou D Eur J Cancer Suppl 2005*

(Level II of evidence)

- **Positive effects of EPO on Hb**
- **Decreasing of need of blood transfusion**
- **Improved QoL**

! …Not specific for HD and NHD….!

- *Rades D et al Cancer 2005*

(Level III of evidence)

- *Henke et al (Lancet 2003)*

(Level I of evidence)

- **Trends towards improved OS**
- **Worsened OS**

We didn't see clear link between the use of ESAs and OS in patients undergoing radio(chemotherapy)!

RT and CT and ESAs?

- "ESAs in oncology: a study level meta-analysis of survival and other safety outcomes"

  (Glaspy et al BJC 2010)

  ⇨ ESAs don't affect mortality or disease progression but increases TEE risk

- ENHANCE *(Henke 2003)*, DAHANCA 10 *(Overgaard 2007)*, GOG-0191 *(Thomas 2008)* , BEST *(Leyland Jones 2005)*, PREPARE *(Amgen 2007 ongoing)*

  ⇨ **TARGET:** Hb values over 13g/dL

  OUT OF RECOMMENDATION!

ANAEMIA MANAGEMENT FOR PATIENTS WITH LYMPHOID MALIGNANCIES

- **ONSET: 82% at presentation 55-88% following CT**

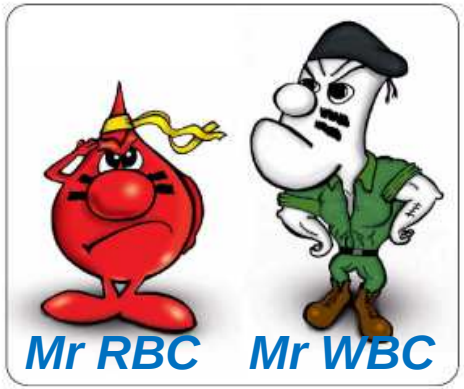
(Henry DH Drugs 2007)

- **Under development:**

- **CERA :** continuous erythropoietin recepetor activator
- **CNTO :** synthetic peptide-based erythropoiesis-stimulating agen
- **FG-2216 :**small molecule-inhibitor of HIF

CONCLUSIONS:

- Usefulness of Guidelines Recommendations
- FN and anemia management
- Hospitalization's reduction
- New clinical trials




Thank you!