GLI AIUTI: Terapia di supporto

Dr. Fausto Petrelli

UO Oncologia

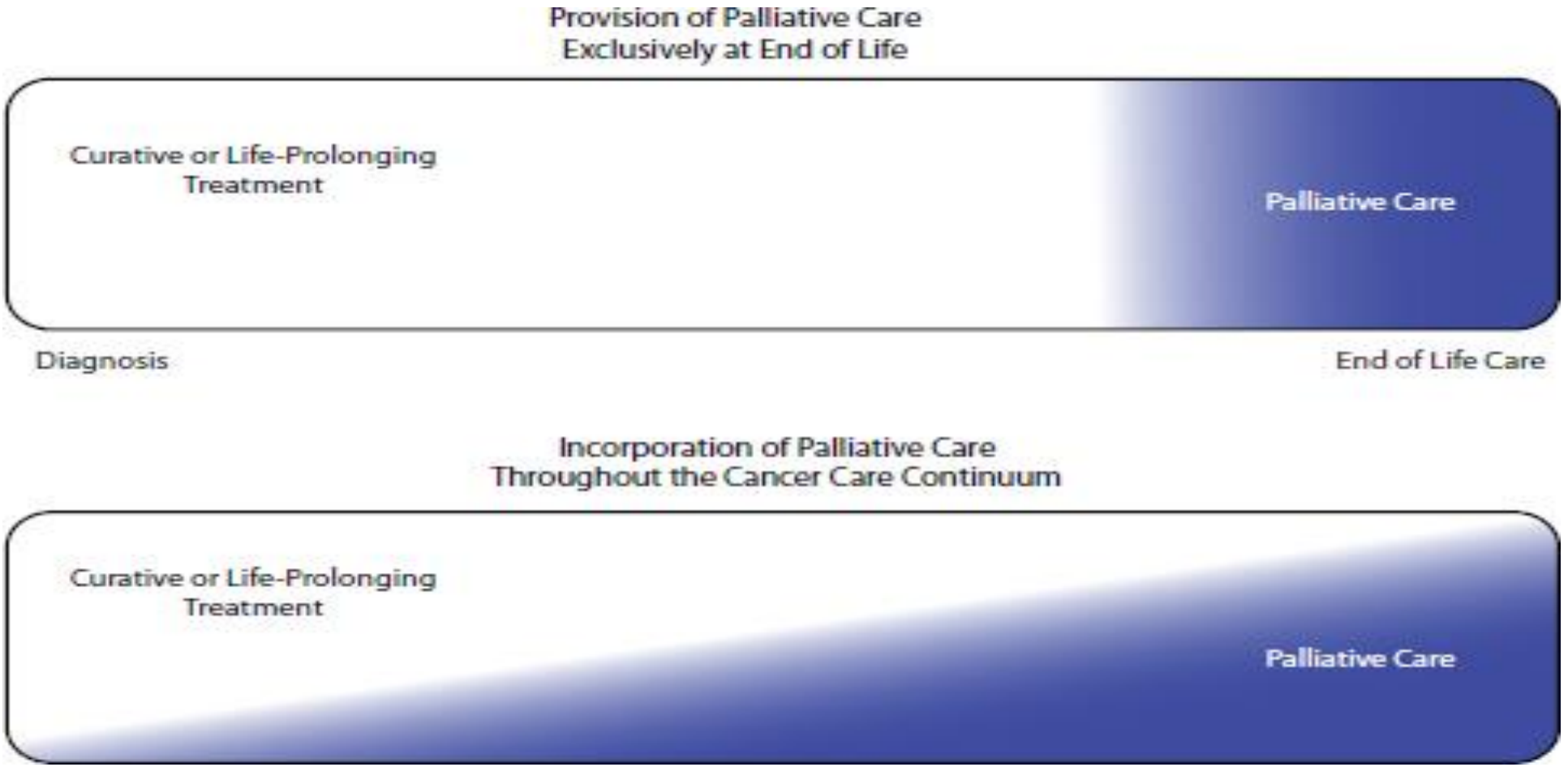
ASST Bergamo Ovest

Treviglio (BG)

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

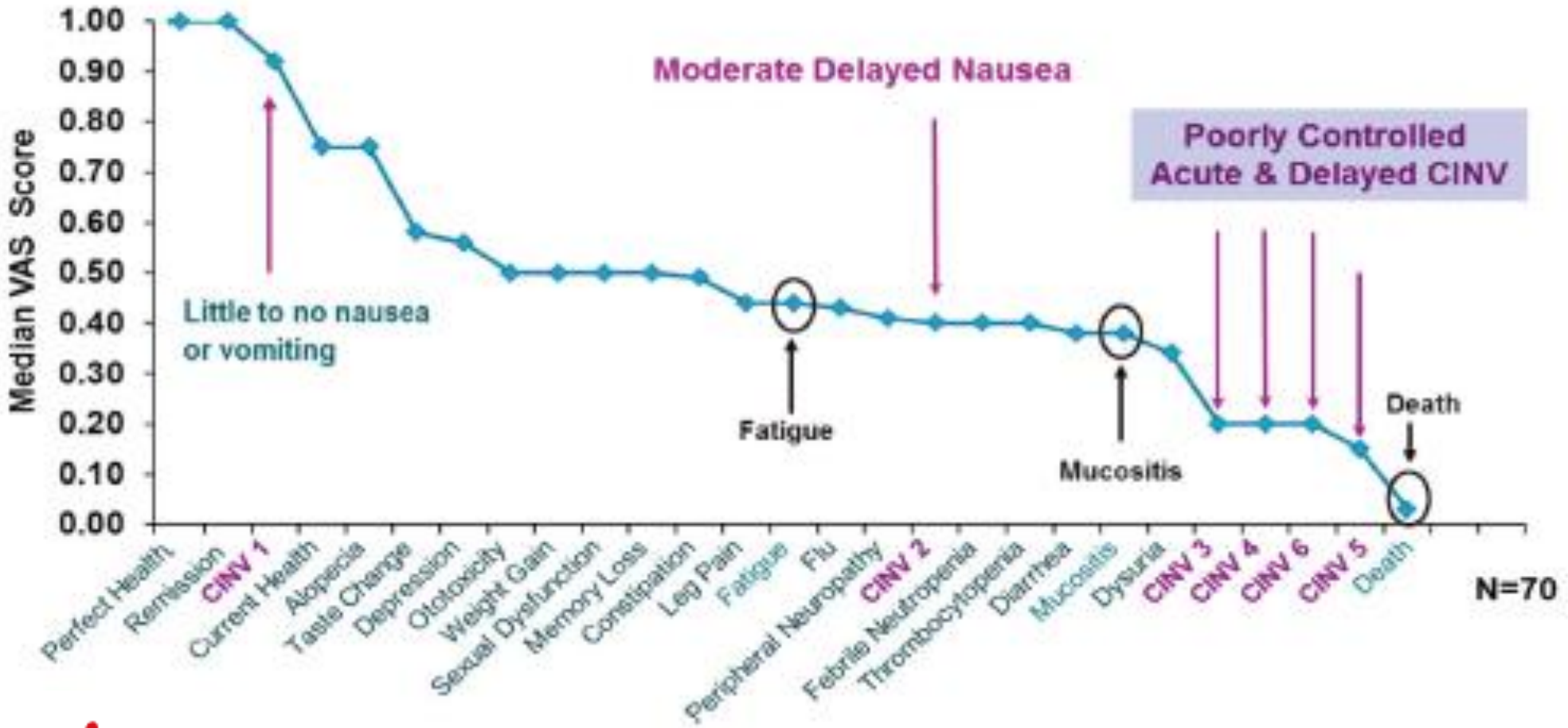
Ruolo delle early palliative care



Terapia di supporto in oncologia: agenda

- Nausea e vomito
- Anemia:
  - ✓Ferro
  - ✓EPO
- Mielodepressione:
  - ✓G-SCF
- Alopecia

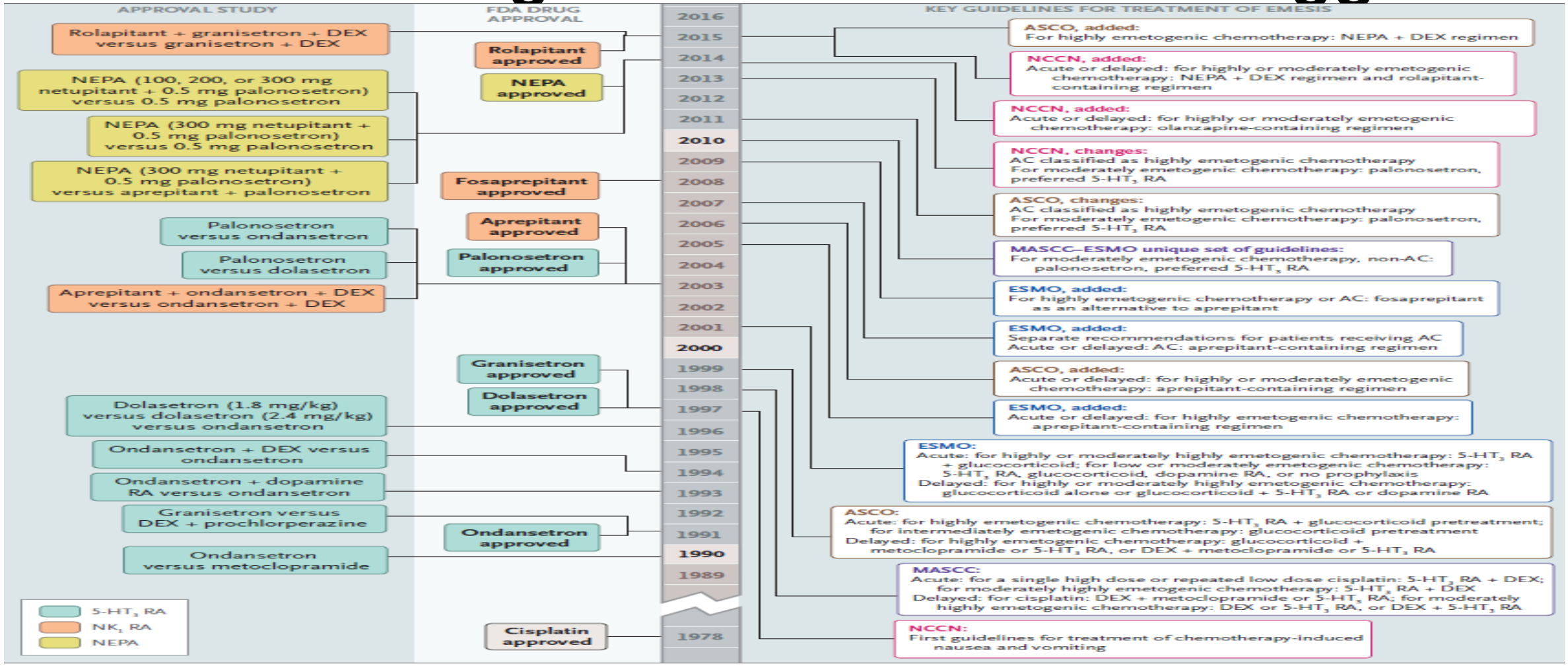
Nausea e vomito: la percezione del paziente



Nausea e vomito: classificazione del rischio

High Emetogenic Risk† (> 90%‡)	Moderate Emetogenic Risk (30% to 90%‡)	Low Emetogenic Risk (10% to 30%‡)	Minimal Emetogenic Risk (< 10%‡)
• Anthracycline (doxorubicin or epirubicin) and cyclophosphamide combination (A/C) • Carmustine > 250 mg/m² • Cisplatin • Cyclophosphamide > 1500 mg/m² • Dacarbazine • Doxorubicin ≥ 60 mg/m² • Epirubicin > 90 mg/m² • Ifosfamide ≥ 2 g/m² per dose • Mechlorethamine • Streptozocin	• Aldesleukin > 12 million to 15 million IU/m² • Amifostine > 300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin§ • Carmustine§ ≤ 250 mg/m² • Clofarabine • Cyclophosphamide ≤ 1500 mg/m² • Cytarabine > 200 mg/m² • Dactinomycin§ • Daunorubicin§ • Doxorubicin§ < 60 mg/m² • Epirubicin§ ≤ 90 mg/m² • Idarubicin • Ifosfamide§ < 2 g/m² per dose • Interferon α ≥ 10 million IU/m² • Irinotecan§ • Melphalan • Methotrexate§ ≥ 250 mg/m² • Oxaliplatin • Temozolomide	• Ado-trastuzumab emtansine • Aldesleukin ≤ 12 million IU/m² • Amifostine ≤ 300 mg/m² • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Cytarabine (low dose) 100 mg/m² to 200 mg/m² • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil • Floxuridine • Gemcitabine • Interferon α > 5 million but < 10 million IU/m² • Ixabepilone • Methotrexate > 50 but < 250 mg/m² • Mitomycin • Mitoxantrone • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Thiotepa • Topotecan • Ziv-aflibercept	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine < 100 mg/m² • Decitabine • Denileukin diftitox • Dexrazoxane • Fludarabine • Interferon α ≤ 5 million IU/m² • Ipilimumab • Methotrexate ≤ 50 mg/m² • Nelarabine • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pertuzumab • Rituximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

La storia degli antiemetici fino ad oggi



Navari & Aapro, NEJM 2016

Scale di valutazione

Table 3. Risk scoring algorithm for ≥grade 2 CINV in cancer patients receiving chemotherapy

Predictive factor	Before a cycle of chemotherapy
Baseline score	10
Impact of patient risk factors	
Patient < age	+1
Patient expects to have CINV	+1
Patient slept <7 h the night before chemotherapy	+1
Patient has a history of morning sickness	+1
Patient is about to receive platinum or anthracycline chemotherapy	+2
Patient on-prescription antiemetics are used at home in the prior cycle	+3
Patient had nausea or vomiting in the prior cycle	+5
About to receive the 2nd cycle	−5
About to receive ≥ 3rd cycle	−6
Total composite risk score[a]	?

Table 4. Detailed analysis of risk scoring system for ≥grade 2 CINV

Score cut point	Observed prevalence[a] (%)	Sensitivity (%)	Specificity (%)	Likelihood ratio[b]
<8	12.5	100	0	1.0
≥8 to <12	13.6	99.8	1.2	1.01
≥12 to <16	23.1	97.9	10.7	1.10
≥16 to <20[a]	43.7	87.4	38.4	1.42
≥20 to <24	57.6	51.2	75.7	2.11
≥24 to <28	72.8	18.8	94.8	3.60
≥28	87.9	2.1	99.8	9.08

Sistema Socio Sanitario Regione Lombardia ASST Bergamo Ovest

Oncologia Medica Treviglio

Dranitsaris et al, Ann Oncol 2017

Tricco et al. BMC Medicine (2016) 14:216
DOI 10.1186/s12916-016-0761-9

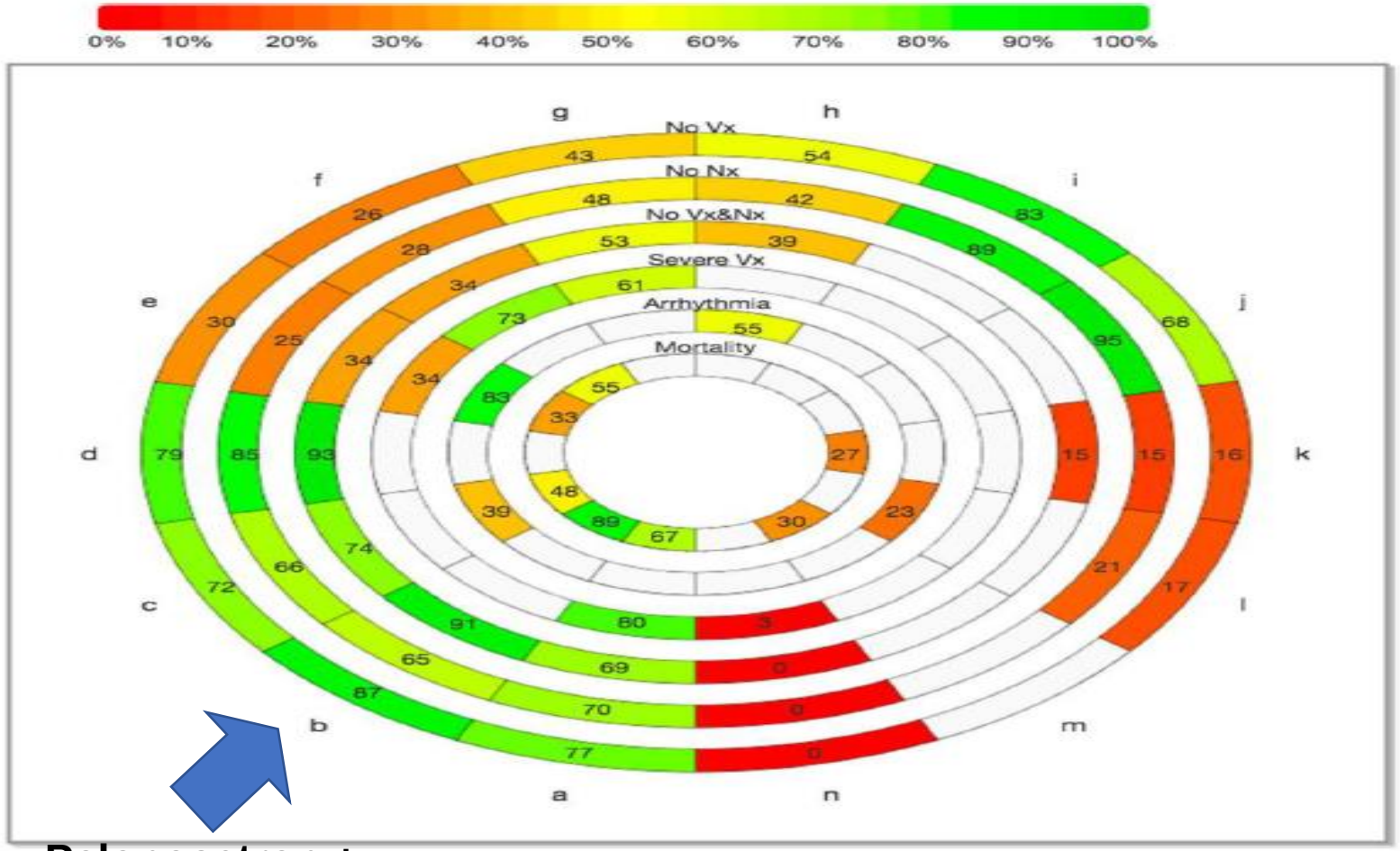
BMC Medicine

5HT-3 antagonisti: palonosetron vs ONDA

RESEARCH ARTICLE Open Access

Treatments
a: ONDA+STER
b: PALO+STER
c: GRAN+STER
d: RAMO+STER
e: GRAN
f: ONDA
g: RAMO
h: PALO
i: TROP+STER
j: DOLA+STER
k: TROP
l: DOLA
m: METO+DEX
n: PLAC

Outcomes
Circles from outside in refer to :
1st: No Vx
2nd: No Nx
3rd: No Vx&Nx
4th: Severe Vx
5th: Arrhythmia
6th: Mortality
White sectors refer to treatments without data on the outcome within the circle.

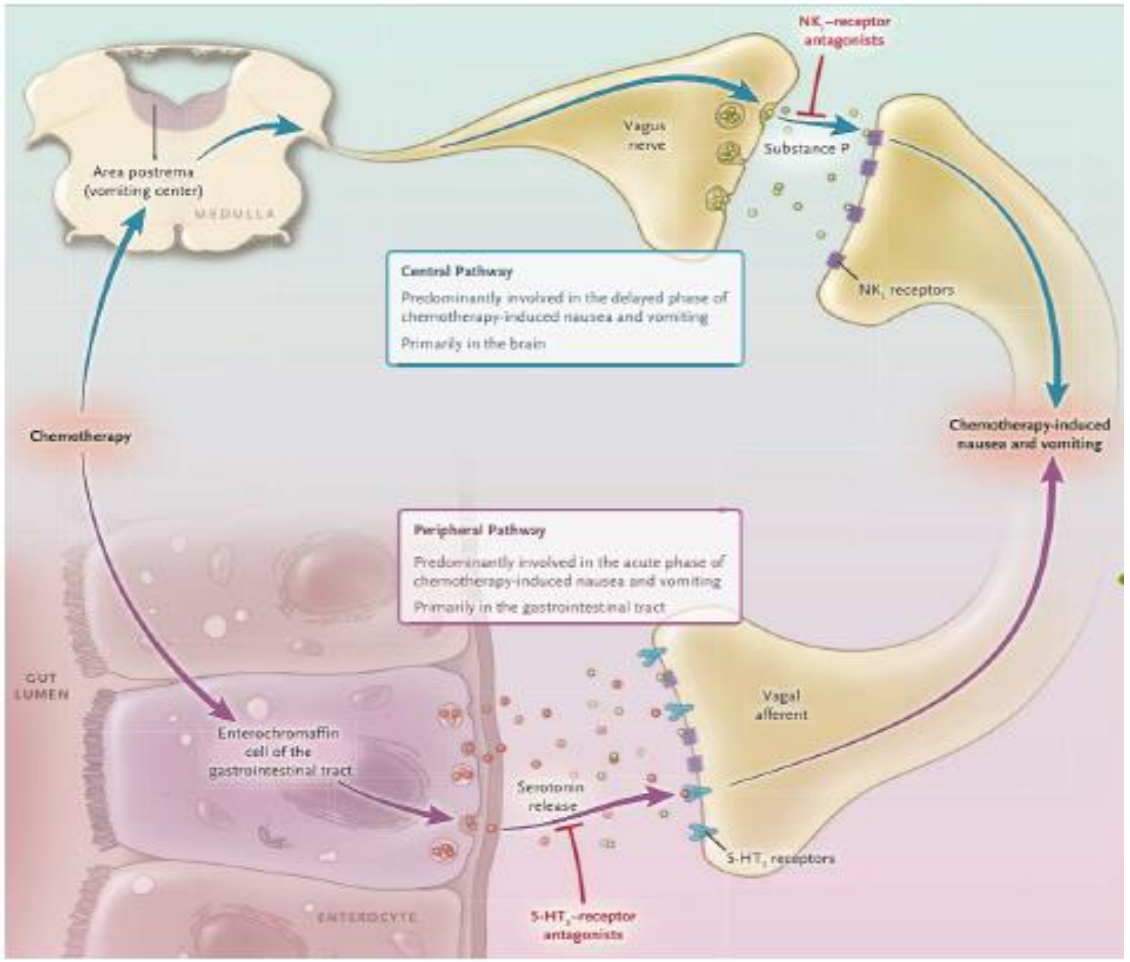


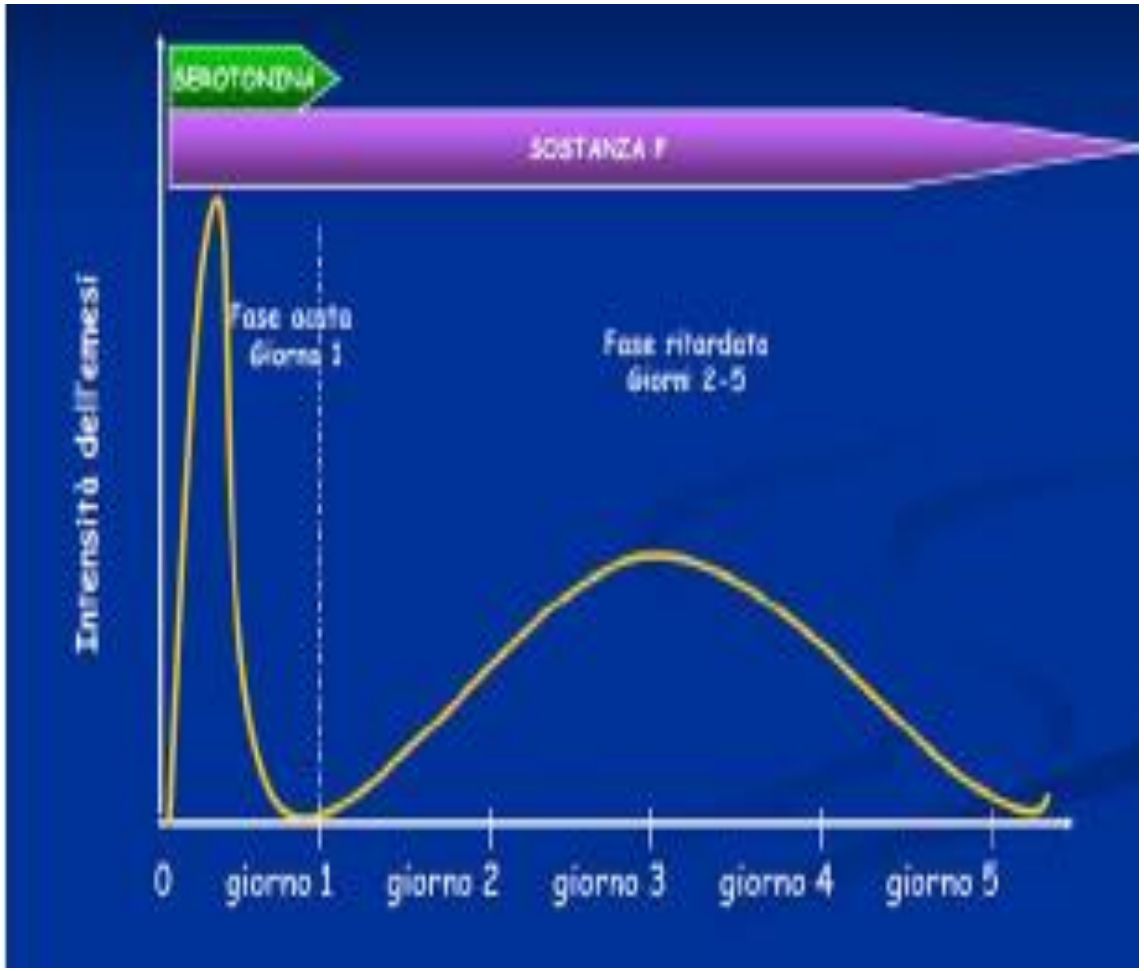
Palonosetron + desametasone

Sistema Sociosanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

NK-1 antagonisti: razionale





Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest
Oncologia Medica Treviglio

NK-1 vs regimi standard

OXFORD

JNCI J Natl Cancer Inst (2017) 109(2): djw217

doi: 10.1093/jnci/djw217
First published online October 30, 2016
Article

ARTICLE

Neurokinin-1 Receptor Antagonist-Based Triple Regimens in Preventing Chemotherapy-Induced Nausea and Vomiting: A Network Meta-Analysis

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

Zhang et al; JNCI 2017

Triplice terapia (DESA + NK-1 + 5HT-3)

AKYNZEO

- **Netupitant** 300 mg
- **PALO** 0,5 mg

- **Netupiant:** new highly selective antagonist of the P-substance receptor
- Can saturate NK1-R up to 90%
- Long half life (96 h) compared to Arepitant (9-13h)

Linee guida

MASCC/ESMO Guidelines

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT_3 + DEX + NK_1
High AC	5-HT_3 + DEX + NK_1
Carboplatin	5-HT_3 + DEX + NK_1
Moderate (other than carboplatin)	5-HT_3 + DEX
Low	5-HT_3 or DEX or DOP
Minimal	No routine prophylaxis

5-HT_3 = serotonin$_3$ receptor antagonist; DEX = DEXAMETHASONE; NK_1 = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron); DOP = dopamine receptor antagonist

NOTE: If the NK_1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.

Multinational Association of Supportive Care in Cancer
Supportive Care Makes Excellent Cancer Care Possible

MASCC www.mascc.org ESMO

MASCC website. MASCC/ESMO Antiemetic Guideline 2016.

ASCO GUIDELINES

ANTIEMETICS: AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE UPDATE		
Clinical Question	Recommendation	Evidence Rating
What is the optimal treatment to prevent nausea and vomiting from high-emetic-risk antineoplastic agents in adults who receive single-day antineoplastic agent therapy?	Adult patients treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of a neurokinin 1 (NK_1) receptor antagonist, a serotonin (5-HT_3) receptor antagonist, dexamethasone, and olanzapine. Dexamethasone and olanzapine should be continued on days 2 to 4.	Type: evidence based, benefits outweigh harms Quality of evidence: high Strength of recommendation: strong
	Adult patients treated with an anthracycline combined with cyclophosphamide (AC) should be offered a four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine. Olanzapine should be continued on days 2 to 4.	Type: evidence based, benefits outweigh harms Quality of evidence: high Strength of recommendation: strong

Olanzapina

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting

Rudolph M. Navari, M.D., Rui Qin, Ph.D., Kathryn J. Ruddy, M.D., Heshan Liu, Ph.D., Steven F. Powell, M.D., Madhuri Bajaj, M.D., Leah Dietrich, M.D., David Biggs, M.D., Jacqueline M. Lafky, M.S., and Charles L. Loprinzi, M.D.

E' attiva sui recettori della dopamina (D1, D2 e D4), su alcuni sottotipi di recettori della serotonina (5-HT2A, 5-HT2C e 5-HT3), sul recettore alfa1 adrenergico, sui recettori della muscarina M1 e sul recettore dell'istamina H1 (Lancet, 1997).

Navari et al; NEJM 2016

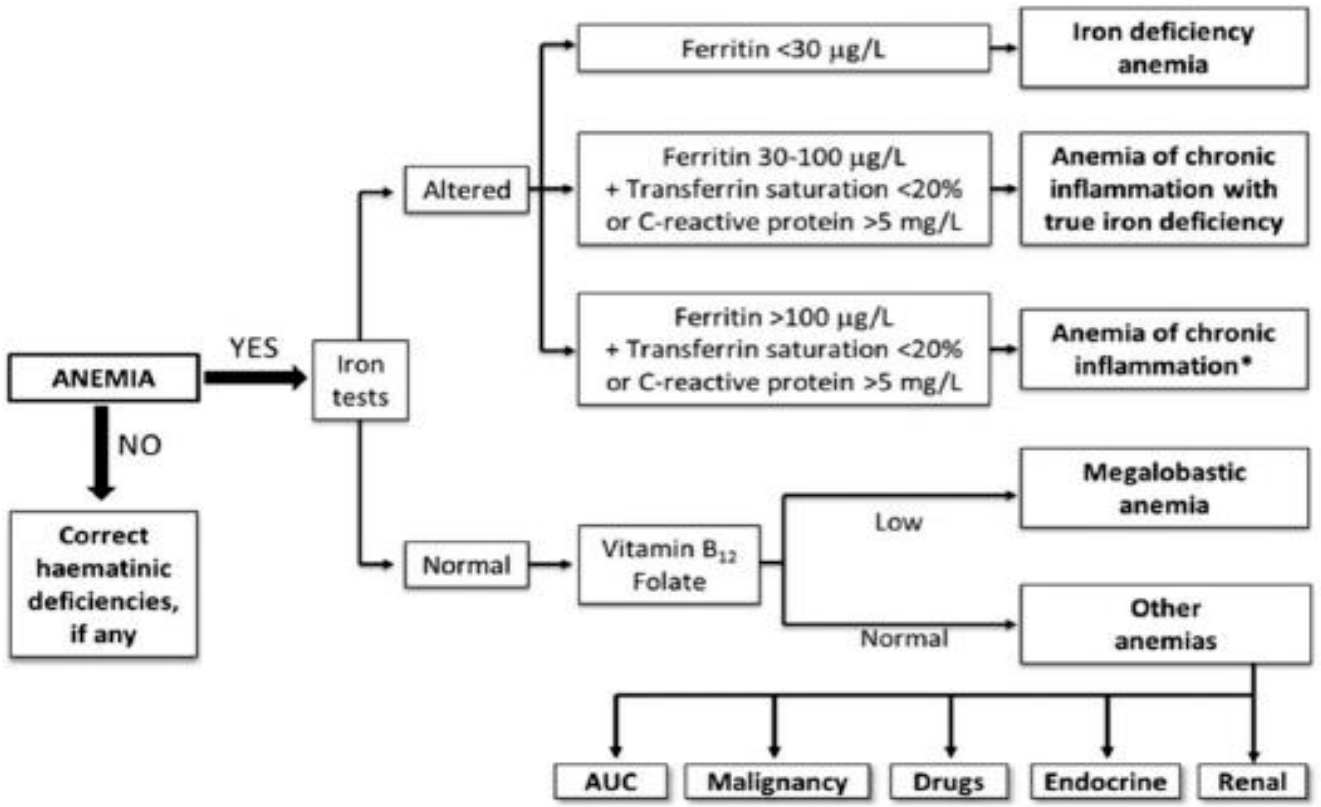
triplice terapia ± olanzapina (DESA + 5HT3 + anti-NK1)

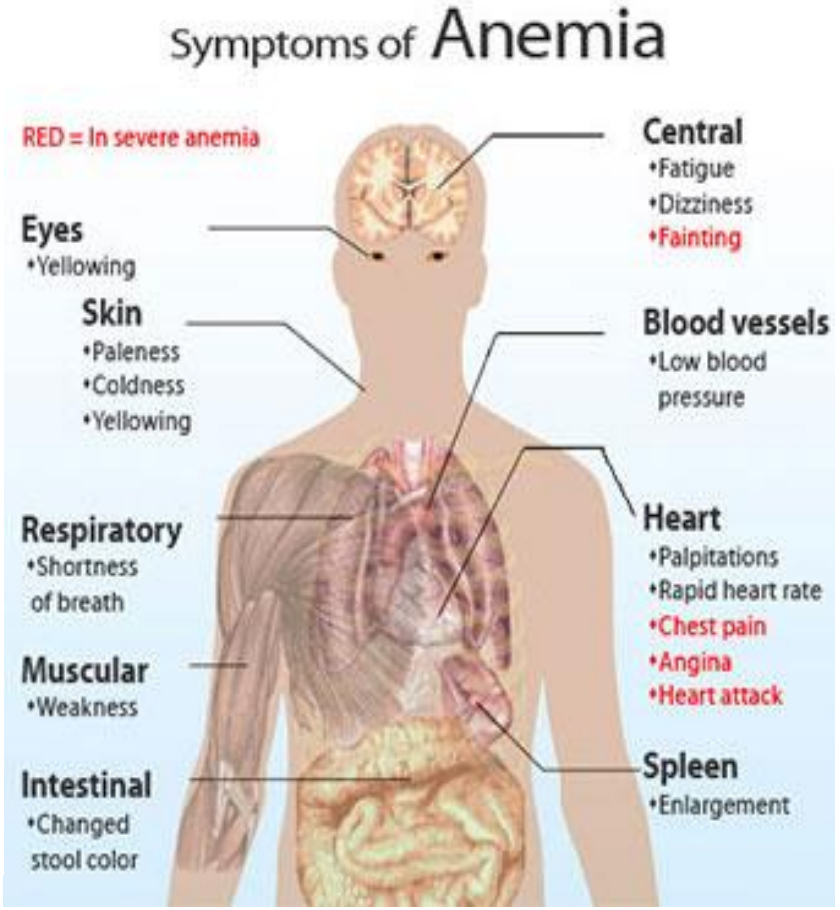
Navari et al Study Findings

	Olanzapine, % (N=192)	Placebo, % (N=188)	*P* Value
No Nausea			
At 24 h	74	45	.002
25 to 120 h	42	25	.002
Overall	37	22	.002
CR Rate			
At 24 h	86	65	<.001
25 to 120 h	67	52	.007
Overall	64	41	<.001

Navari RM, et al. *N Engl J Med*. 2016;375:134-142.

Anemia e cancro

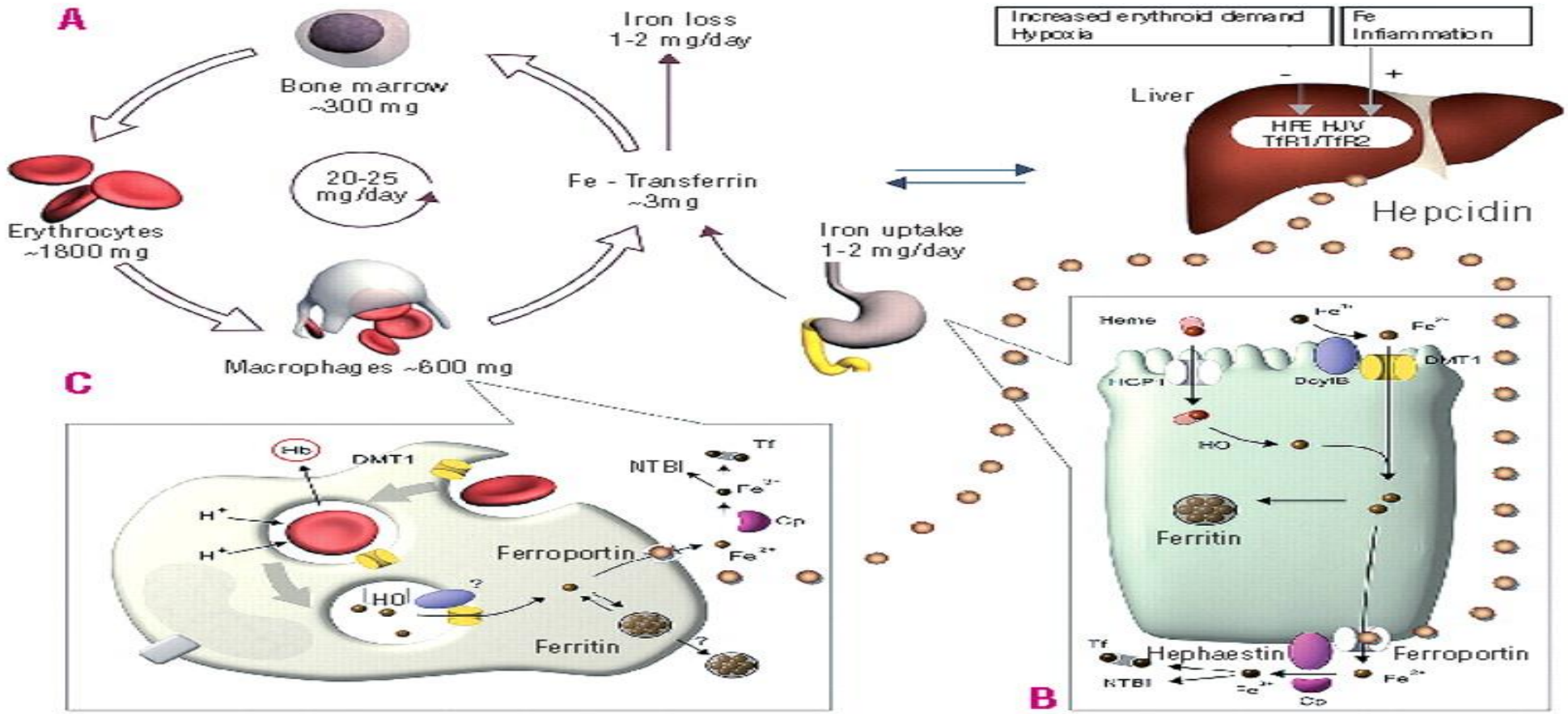




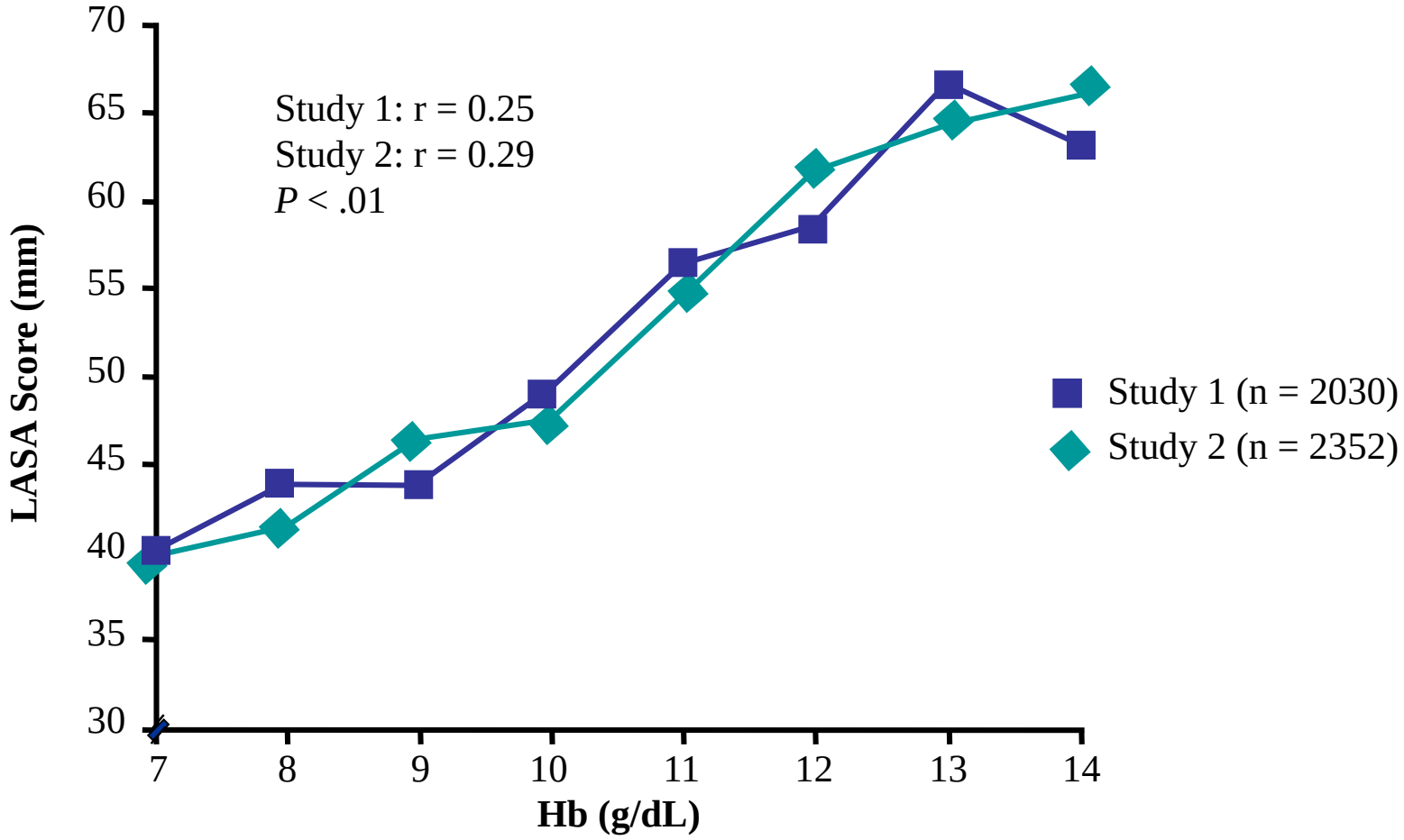
Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

Anemia e infiammazione



Correlazione Hb e qualità di vita

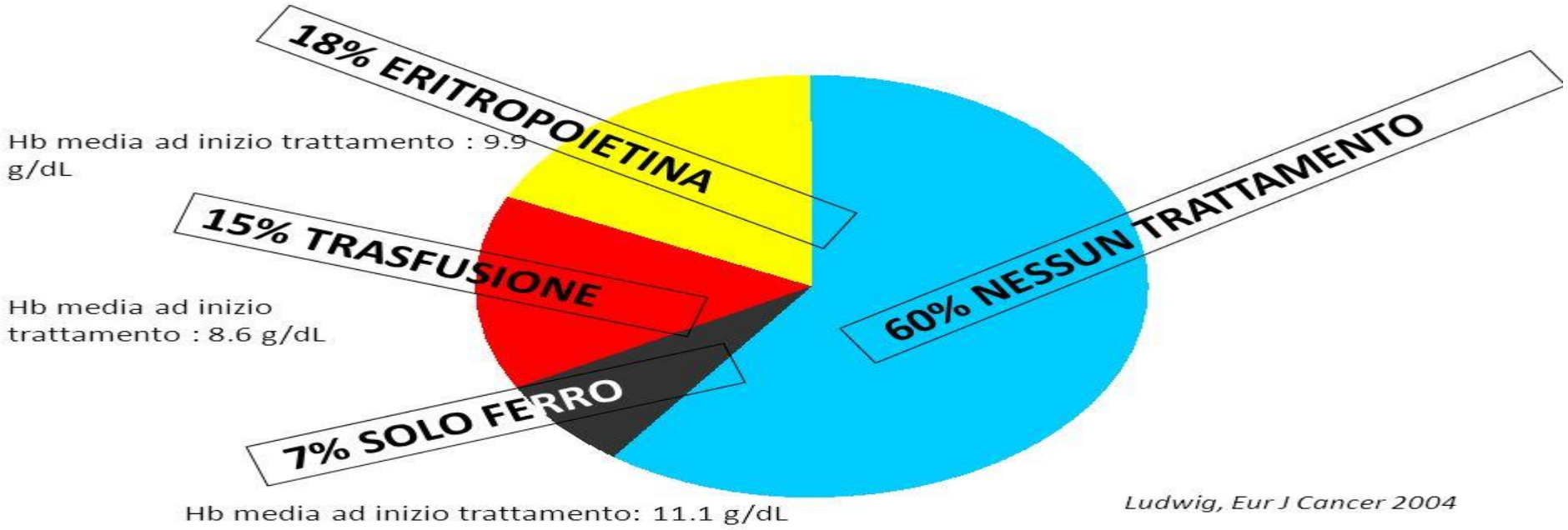


Crawford J, et al. Cancer. 2002;15:888-895.

Anemia in oncologia: la gestione

Trattamento dei pazienti anemici
Survey europea su oltre 15.000 pazienti oncologici

Mediamente il 67% dei pazienti oncologici sviluppa anemia



Ludwig, Eur J Cancer 2004

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

EPO e anemia da CT: trasfusioni

Cochrane Library
Cochrane Database of Systematic Reviews

6 Participants receiving red blood cell transfusions - different therapies	88	16093	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.62, 0.68]
6.1 chemotherapy	71	13405	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.61, 0.67]
6.2 radio/radiochemotherapy	6	693	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.34, 0.58]
6.3 no therapy	10	1774	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.72, 0.91]
6.4 unclear/other	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.99]

-36% di rischio trasfusione

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

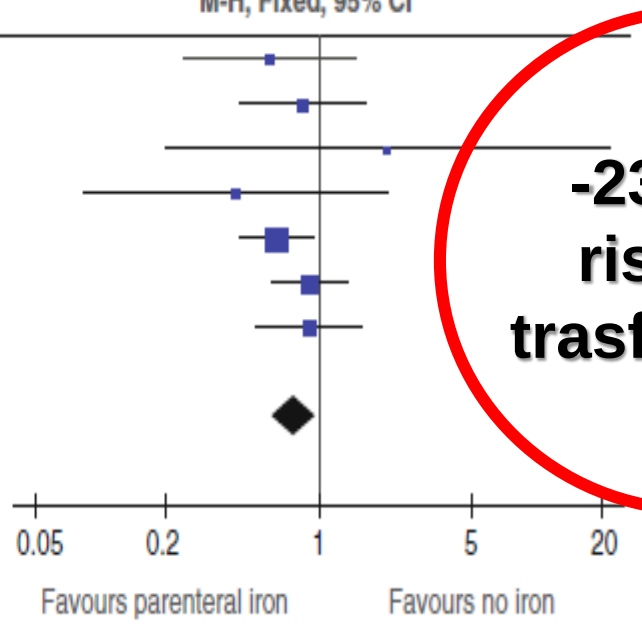
Oncologia Medica Treviglio

Ferro + ESA: meta-analisi

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Auerbach 2004	9	78	7	36	7.0%	0.59 [0.24, 1.47]	2004
Henry 2007a	11	41	14	44	9.9%	0.84 [0.43, 1.64]	2007
Hedenus 2007	2	33	1	34	0.7%	2.06 [0.20, 21.65]	2007
Pedrazzoli 2008	2	73	5	76	3.6%	0.42 [0.08, 2.08]	2008
Bastit 2008	32	200	49	196	36.2%	0.64 [0.43, 0.95]	2008
Auerbach 2010	32	116	37	122	26.4%	0.91 [0.61, 1.36]	2010
Steensma 2011	20	164	22	163	16.2%	0.90 [0.51, 1.59]	2011
Total (95% CI)		705		671	100.0%	0.77 [0.62, 0.97]	
Total events	108		135				

Heterogeneity: $Chi^2 = 3.42$, $df = 6$ ($P = 0.75$); $I^2 = 0\%$

Test for overall effect: $Z = 2.25$ ($P = 0.02$)



-23% di rischio trasfusione

Fig. 4 Forest plot for RR of transfusion with parenteral iron

Sistema Socio Sanitario Regione Lombardia ASST Bergamo Ovest

Oncologia Medica Treviglio

Petrelli et al; JCRCO 2012

Ferro e anemia da chemioterapia: rischio trasfusioni (Cochrane 2016)

Analysis 1.2. Comparison 1 Benefits and harms of iron supplementation, Outcome 2 RBC transfusion.

Review: The role of iron in the management of chemotherapy-induced anemia in cancer patients receiving erythropoiesis-stimulating agents

Comparison: 1 Benefits and harms of iron supplementation

Outcome: 2 RBC transfusion

Study or subgroup	ESA+Iron n/N	ESA n/N	Risk Ratio M,Random,95% CI	Weight	Risk Ratio M,Random,95% CI
Auerbach 2004a	5/41	3/12		2.9 %	0.49 [0.14, 1.75]
Auerbach 2004b	4/37	2/12		1.9 %	0.65 [0.14, 3.11]
Auerbach 2004c	3/43	2/12		1.7 %	0.42 [0.08, 2.23]
Auerbach 2010	32/116	37/122		29.4 %	0.91 [0.61, 1.36]
Bastit 2008	32/200	49/196		29.3 %	0.64 [0.43, 0.95]
Beguin 2008	2/50	4/52		1.7 %	0.52 [0.10, 2.71]
Henry 2007a (1)	11/63	7/31		6.6 %	0.77 [0.33, 1.80]
Henry 2007b	6/61	7/32		4.7 %	0.45 [0.16, 1.23]
Pedrazzoli 2008	2/73	5/76		1.8 %	0.42 [0.08, 2.08]
Steensma 2011a	20/164	11/81		10.0 %	0.90 [0.45, 1.78]
Steensma 2011b	21/163	11/82		10.1 %	0.96 [0.49, 1.89]
Total (95% CI)	**1011**	**708**		**100.0 %**	**0.74 [0.60, 0.92]**

Total events: 138 (ESA+Iron), 138 (ESA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.91$, df = 10 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 2.70 (P = 0.0069)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours ESA+Iron Favours ESA

-26% di rischio trasfusione

Sistema Socio Sanitario Regione Lombardia ASST Bergamo Ovest

Oncologia Medica Treviglio

Mhaskar et al, Cochrane Library 2016

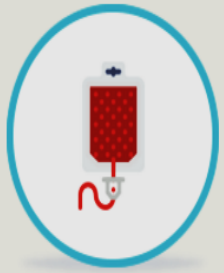
PBM: patient blood management

ONLY ONE
UNA TRASFUSIONE
UNA DECISIONE CLINICA
INDIPENDENTE

Gli obiettivi del PBM

Il Patient Blood Management (PBM) è una strategia multidisciplinare e multimodale che mette al centro la salute e la sicurezza del paziente e migliora i risultati clinici basandosi sulla risorsa sangue dei pazienti stessi. Questo approccio riduce in modo significativo l'utilizzo dei prodotti del sangue, affrontando tutti i fattori di rischio trasfusionale modificabili ancor prima che sia necessario prendere in considerazione il ricorso alla terapia trasfusionale stessa.
Gli obiettivi del PBM sono:

Miglioramento degli *outcome* clinici



Prevenzione della trasfusione evitabile

Riduzione dei costi di gestione

Ministero della Salute Istituto Superiore di Sanità Centro Nazionale Sangue	LINEE GUIDA PER IL PROGRAMMA DI PATIENT BLOOD MANAGEMENT	LG CNS 05 Rev. 0 27.10.2016

EMANA LA SEGUENTE LINEA GUIDA

	Raccomandazioni da adottare nel periodo pre-operatorio, intra-operatorio e post-operatorio
1	I pazienti con coagulopatie e/o piastrinopatie congenite o acquisite, o anamnesi positiva per emorragia, o in trattamento con anticoagulanti e/o antiaggreganti piastrinici, sono gestiti in tutte le fasi in collaborazione con un esperto di emostasi e trombosi.
2	In tutti i pazienti adulti, candidati a terapia trasfusionale con concentrati eritrocitari (omologhi o autologhi), ospedalizzati ed emodinamicamente stabili, inclusi quelli critici, quelli con precedenti patologie cardiovascolari e quelli candidati ad interventi di chirurgia ortopedica o cardiaca, è raccomandata l'adozione di una soglia trasfusionale restrittiva, stabilita in collaborazione con un esperto di medicina trasfusionale.
3	La soglia trasfusionale da adottare per la terapia con concentrati eritrocitari (omologhi o autologhi) in altre categorie di pazienti è stabilita in collaborazione con un esperto di medicina trasfusionale.
4	Nei pazienti ospedalizzati e clinicamente stabili, in caso di necessità di trasfusione di concentrati eritrocitari (omologhi o autologhi), è trasfusa una sola unità alla volta; la scelta relativa ad un'ulteriore trasfusione deve essere supportata da una attenta rivalutazione clinica del paziente.
5	Nei pazienti con piastrinopenia o disfunzione piastrinica acquisita o in presenza di coagulazione intravascolare disseminata acuta sottoposti ad interventi di chirurgia maggiore elettiva per i quali esiste un elevato rischio emorragico o il rischio di sanguinamento in sedi critiche, si suggerisce di prendere in considerazione la trasfusione profilattica di concentrati piastrinici. La definizione della soglia trasfusionale e delle tempistiche e modalità della terapia trasfusionale sono stabilite in collaborazione con un esperto di medicina trasfusionale.
6	Le indicazioni ad un programma di autotrasfusione mediante predeposito sono conformi alla normativa vigente.
7	Il volume e la frequenza dei prelievi per campioni ematici destinati alla diagnostica di laboratorio sono contenuti al fine di prevenire l'anemia iatrogena.

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

Strategie trasfusionali: mortalità, unità utilizzate e costi

bjh research paper

Impact of red blood cell transfusion strategies in haemato-oncological patients: a systematic review and meta-analysis

Table V. Costs.

Reference	RBC transfusion strategy	Reduction of costs due to reduction in RBC use
Allameddine *et al* (2015)	Single- versus double-unit	€40 000 per year per haematology hospital ward
Berger *et al* (2012)	Single- versus double-unit	€2534 per patient per therapy cycle†
Lightdale *et al* (2012)	Hb trigger: 70 g/l vs. 90 g/l	€1278 per HSCT patient†
Paananen *et al* (2009)	Hb trigger: 80 g/l vs. 90–100 g/l	€335 per patients per whole ALL treatment*

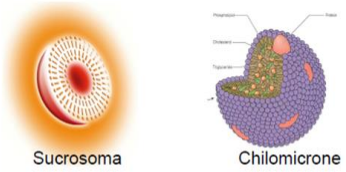
ALL, acute lymphoid leukaemia; Hb, haemoglobin; HSCT, haematopoietic stem cell transplantation; RBC, red blood cell.

*Paediatric RBC units (which are smaller and cheaper) were more often used in the restrictive group compared to the liberal group.

†US dollars were converted to Euros.

Hoecks et al. Br J Hematol 2017

Ferro sucrosomiale + EPO



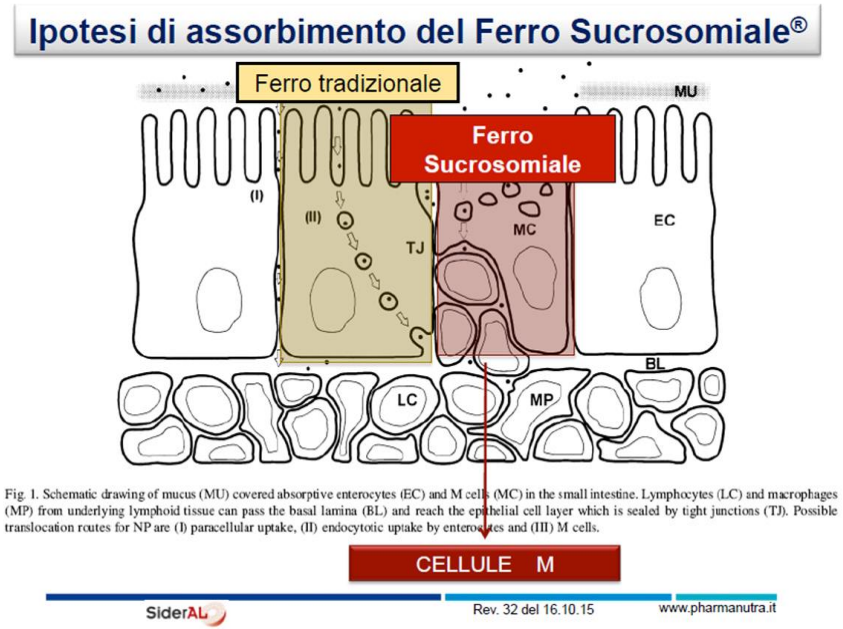


Fig. 1. Schematic drawing of mucus (MU) covered absorptive enterocytes (EC) and M cells (MC) in the small intestine. Lymphocytes (LC) and macrophages (MP) from underlying lymphoid tissue can pass the basal lamina (BL) and reach the epithelial cell layer which is sealed by tight junctions (TJ). Possible translocation routes for NP are (I) paracellular uptake, (II) endocytotic uptake by enterocytes and (III) M cells.

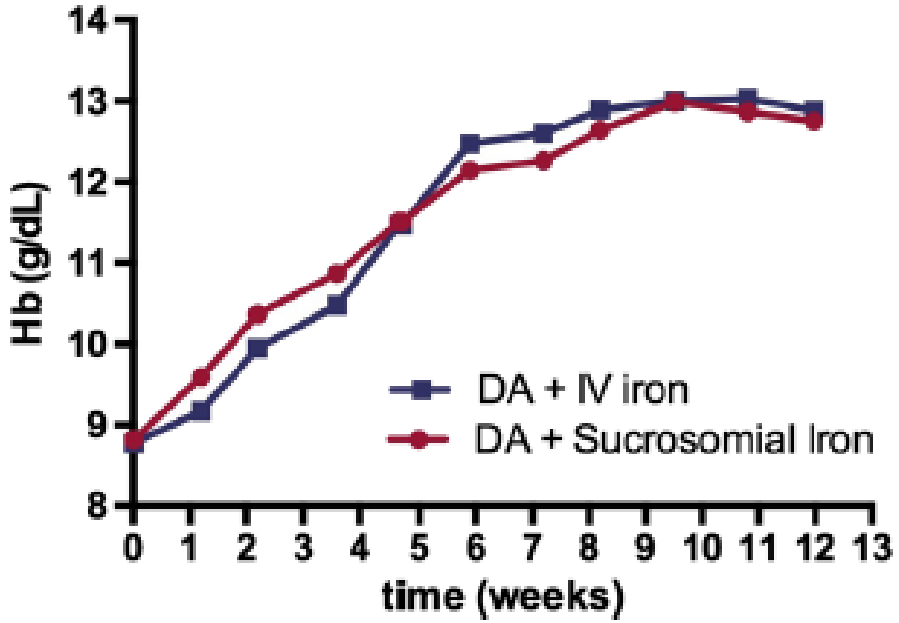


Fig. 1 Hb response in the two treatment groups

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

Maffodda et al, Support Care Cancer 2017

Raccomandazioni

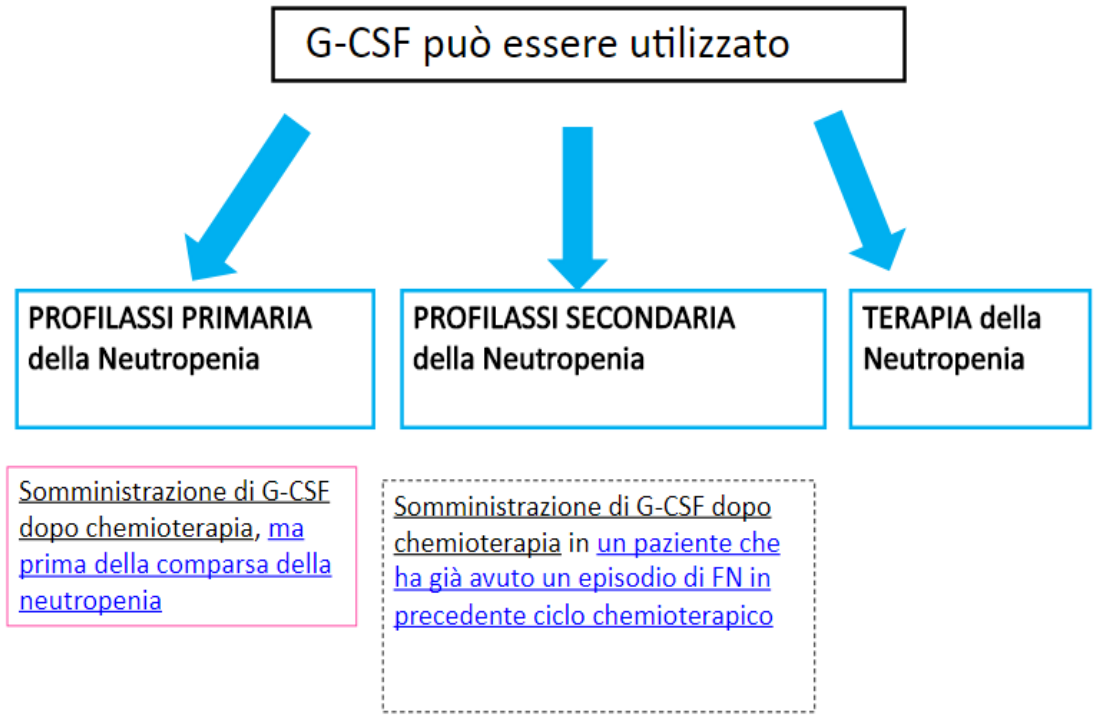
Recommendations	Grade	Quality of evidence
R1. In all cancer patients, but especially in those scheduled for cytotoxic chemotherapy, radiotherapy, or surgery, the presence of anemia and/or iron deficiency should be investigated before and during treatment, to plan the most appropriate therapeutic strategy	1	C
R2. Initial laboratory screening in cancer patients should include, at least, full blood count with reticulocytes, serum ferritin, transferrin saturation, creatinine, and C-reactive protein (CRP)	1	C
R3. In non-anemic ID cancer patients, iron supplements should be administered until serum iron parameters are normalized and iron store replenished, in order to avoid development of anemia	2	C
R4. Patients with curative intent chemotherapy should not receive ESAs for treating chemotherapy-induced anemia	1	B
R5. Patients with palliative chemotherapy-induced anemia should receive adjuvant iron therapy for improving the hematologic response to ESA	1	A
R6. Low-dose oral iron salts may be used to treat ID in cancer patients with less severe anemia	2	B
R7. New oral iron products may be efficacious in patients who are intolerant or non-responsive to conventional iron salts, and in those with contraindications for IV iron	2	B
R8. For ID cancer patients receiving ESAs who are intolerant or non-responsive to oral iron supplementation we recommend the use of IV iron	1	B
R9. For anemic cancer patients with ID, who should not receive ESAs, iron supplementation as monotherapy is recommended	1	C
R10. Medical cancer patient can be managed with restrictive RBCT transfusion trigger (Hb 7–8 g/dL), while a relatively higher trigger may be needed for surgical cancer patients (Hb <9 g/dL). However, those with severe symptomatic or life-threatening anemia should immediately receive RBCT	1	C
R11. In most cases, a single unit transfusion, followed by post-transfusion evaluation to determine the [illegible] units, can be a valid option	2	C
[illegible] of the need for RBCT administration, anemia should be appropriately treated. If indicated, iron and/or ESAs are recommended to treat iron deficit or/and chemotherapy-induced anemia	1	B
R13. In cancer patients with absolute or functional ID, iron supplementation may reduce RBCT and ESA requirements and associated costs	1	B

Barni et al; Expert Rev Hematol 2017

Fattori di crescita mielopoietici: GCSF

- Profilassi primaria neutropenia CT-indotta
- Profilassi secondaria
- Trattamento della NF e della neutropenia
- Mantenimento dose-intensity o dose density
- Riduzione mortalità

Profilassi primaria



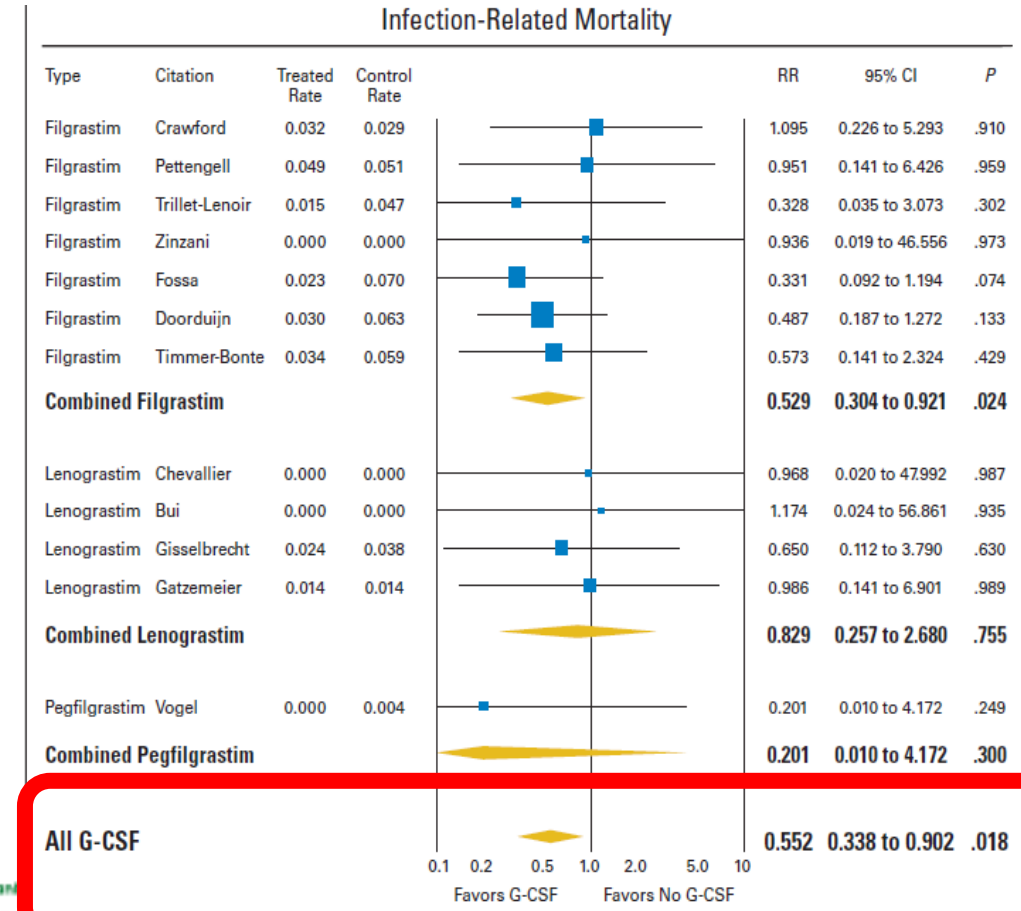
CATEGORIE DI RISCHIO		USO DI G-CSF
1. *CT con rischio di NF attesa*	*≥ 20%*	***Sempre***
2. *CT con rischio di NF attesa*	*10-20%*	***Considerare l'uso di G-CSF*** *(Sì se presenza di altri fattori di rischio)*
3. *CT con rischio di NF attesa*	*≤ 10%*	***Mai*** *(eccetto presenza di alto rischio di gravi complicanza a causa della NF)*

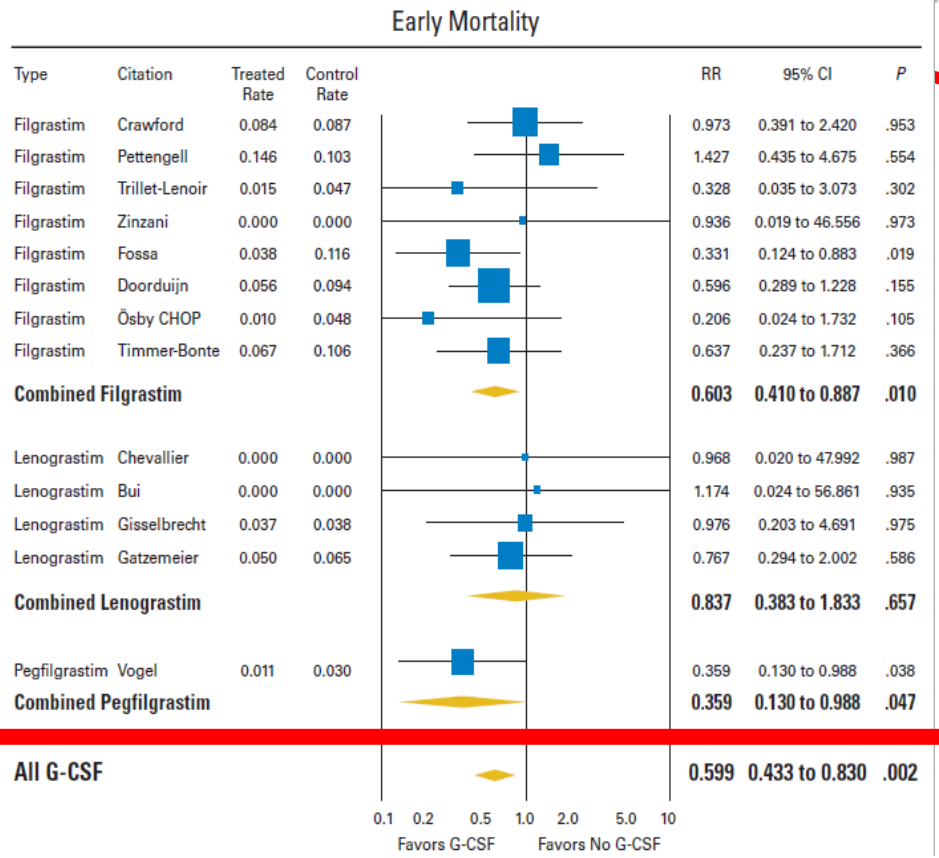
Sistema Socio Sanitario Regione Lombardia ASST Bergamo Ovest

Oncologia Medica Treviglio

Profilassi primaria: infezioni & mortalità

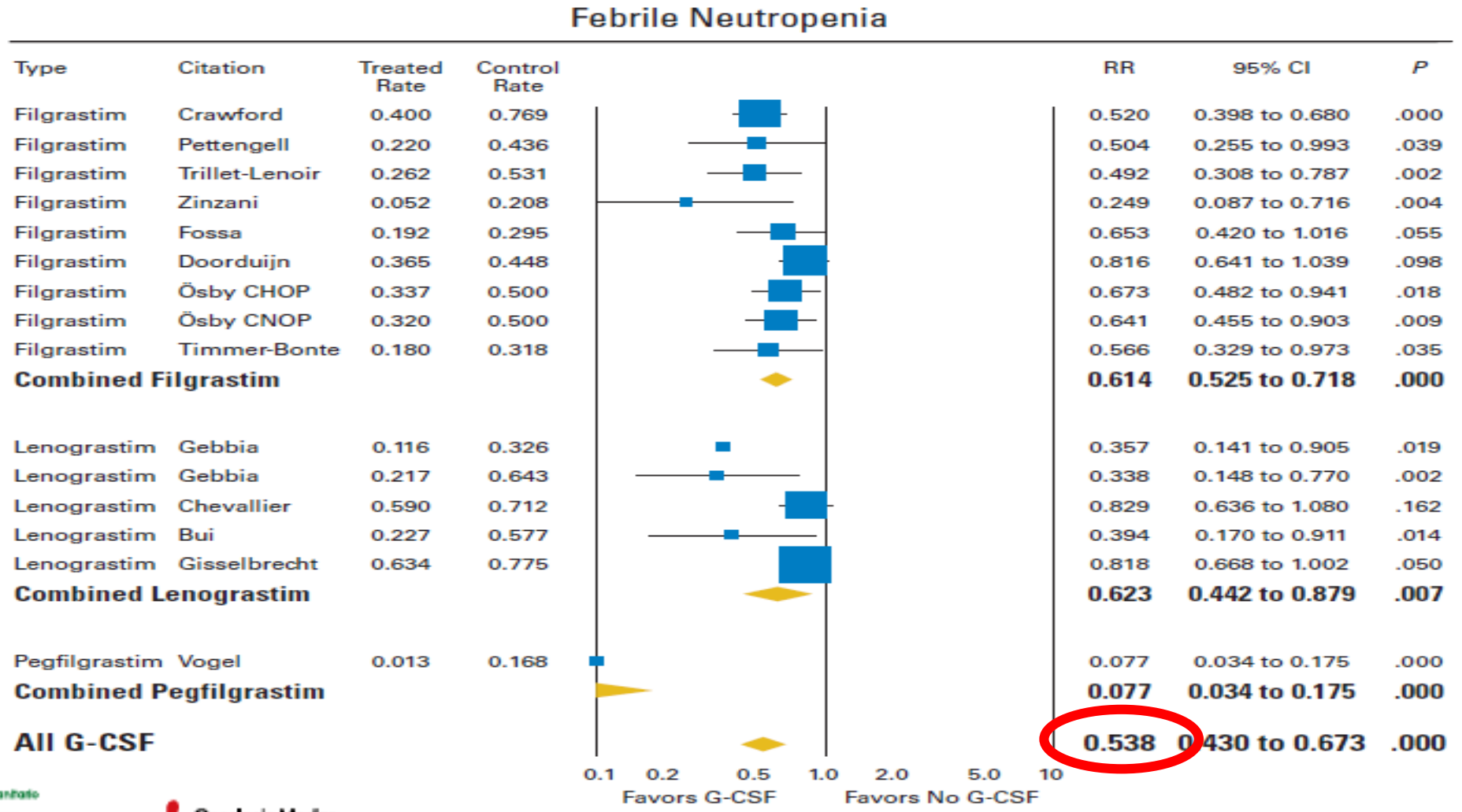
-45% di rischio mortalità infettiva





Kuderer et al; JCO 2007

Profilassi primaria: NF



-50% di rischio NF

Kuderer et al; JCO 2007

Somministrazione

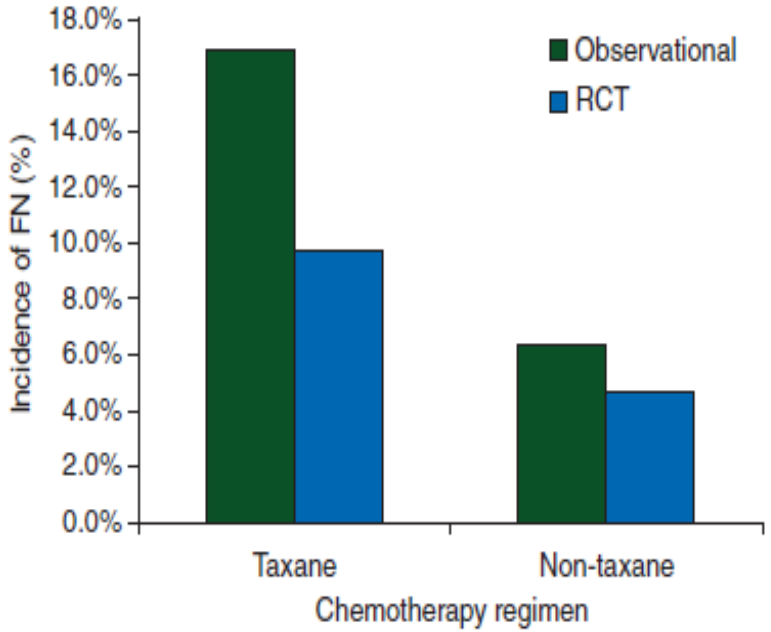
VOLUME 33 · NUMBER 28 · OCTOBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

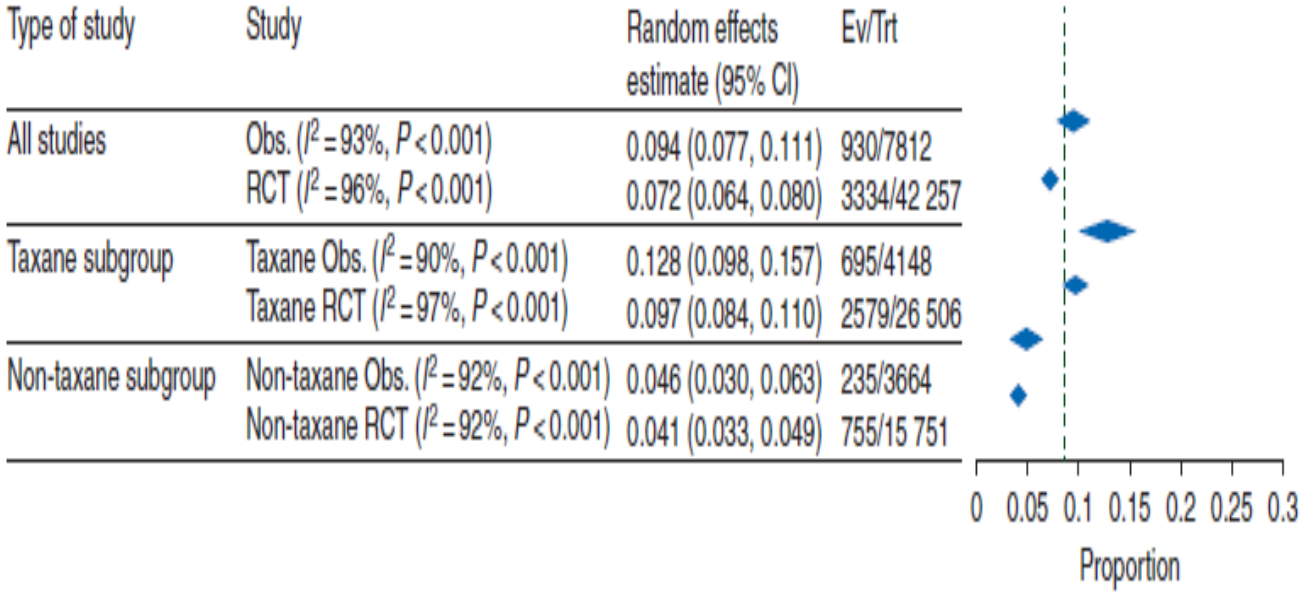
Table 3. Dosing and Administration of CSFs

Agent	Dosing and Administration
Filgrastim	Filgrastim should be started 1 to 3 days after administration of myelotoxic chemotherapy; in setting of high-dose therapy and autologous stem-cell rescue, filgrastim can be started 1 to 5 days after administration of high-dose therapy; filgrastim should be continued until reaching ANC ≥ 2 to 3 × 10^9/L; for PBPC mobilization, filgrastim should be started ≥ 4 days before first leukapheresis procedure and continued until last leukapheresis In adults, recommended filgrastim dose is 5 μg/kg per day for all clinical settings other than PBPC mobilization; in setting of PBPC mobilization, dose of 10 μg/kg per day may be preferable; preferred route of filgrastim administration is subcutaneous
Filgrastim-sndz	Same as for filgrastim
Tbo-filgrastim	Tbo-filgrastim should be started 1 to 3 days after administration of myelotoxic chemotherapy; in adults, recommended tbo-filgrastim dose is 5 μg/kg per day; preferred route of tbo-filgrastim administration is subcutaneous
Pegfilgrastim	Pegfilgrastim 6 mg should be administered once 1 to 3 days after chemotherapy if possible; because some patients will not be able to return for dose of pegfilgrastim because of distance or immobility, for instance, alternatives to consider may include self-administered filgrastim or tbo-filgrastim or same-day pegfilgrastim, recognizing that although same-day pegfilgrastim is not as effective as later pegfilgrastim, it is better than no pegfilgrastim; pegfilgrastrim is also available in a timed automated-inject device that delivers 6 mg of pegfilgrastrim subcutaneously, 27 hours after it is placed on skin and activated; pegfilgrastim is not currently indicated for stem-cell mobilization; 6-mg formulation should not be used in infants, children, or small adolescents who weigh < 45 kg

ASCO guidelines; JCO 2015

Real word vs trial clinici





The FN rates remained significantly higher in the observational study compared with RCT cohorts (OR = 1.74; 95% CI 1.15–2.62; P = 0.012) after adjusting for age, chemotherapy intent, and regimen; this meant that a 13% (95% CI 8.7% to 17.9%) FN rate in RCT would translate into 20% FN rate in observational study.

Truong et al; Ann Oncol 2016

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Oncologia Medica Treviglio

GCSF disponibili

G-CSF	Marchio	Descrizione	Somministrazione	Indicazioni*
Filgrastim	Biograstim® Grastofil® Neupogen® Neutroval® Nivestim® Ratiograstim®Tevagrastim® Zarzio®	Breve durata d'azione, non glicosilato, fattore ricombinante umano stimolante le colonie granulocitarie (G-CSF). (prodotto in *E.coli*)	Singola iniezione SC giornaliera o infusione breve da iniziare 24 ore dopo la chemioterapia e continuando fino a 2 settimane	• Riduzione della durata della neutropenia e dell'incidenza di neutropenia febbrile in pazienti trattati con chemioterapia citotossica • Riduzione della durata della neutropenia in pazienti sottoposti a terapia mieloablativa seguita da trapianto di midollo osseo • Neutropenia cronica grave • Raccolta di cellule progenitrici del sangue periferico • Neutropenia dovuta al Ganciclovir
Lenograstim	Granocyte®	Breve durata di azione, glicosilato, fattore ricombinante umano stimolante le colonie granulocitarie (prodotto in cellule ovariche di criceto cinese)	Singola iniezione SC giornaliera o infusione breve da iniziare 24 ore dopo la chemioterapia, continuata fino a 2 settimane.	• Riduzione della durata della neutropenia e dell'incidenza di neutropenia febbrile in pazienti trattati con chemioterapia citotossica • Riduzione della durata della neutropenia in pazienti sottoposti a terapia mieloablativa seguita da trapianto di midollo osseo • Neutropenia cronica grave • Raccolta di cellule progenitrici del sangue periferico
Pegfilgrastim	Neulasta®	G-CSF umano ricombinante e peghilato a lunga durata d'azione	Singola iniezione da 6 mg SC una sola volta per ciclo di chemioterapia	• Per ridurre la durata della neutropenia e l'incidenza di neutropenia febbrile ad eccezione della leucemia mieloide cronica e delle sindromi mielodisplastiche.
Lipegfilgrastim	Lonquex®	G-CSF glico-metossiPeghilato a lunga durata d'azione	Singola iniezione da 6 mg SC una sola volta per ciclo di chemioterapia	• Riduzione della durata della neutropenia e dell'incidenza di neutropenia febbrile in pazienti adulti trattati con chemioterapia citotossica per neoplasie (con l'eccezione della leucemia mieloide cronica e delle sindromi mielodisplastiche).

Hoggatt J, Pelus LM. *Expert Opin Investig Drugs*. 2013 Sep 27. Epub

Le indicazioni non sono esaustive e possono differire tra biosimilari e tra i paesi. G-CSF: fattore stimolante le colonie di granulociti; SC: sottocute

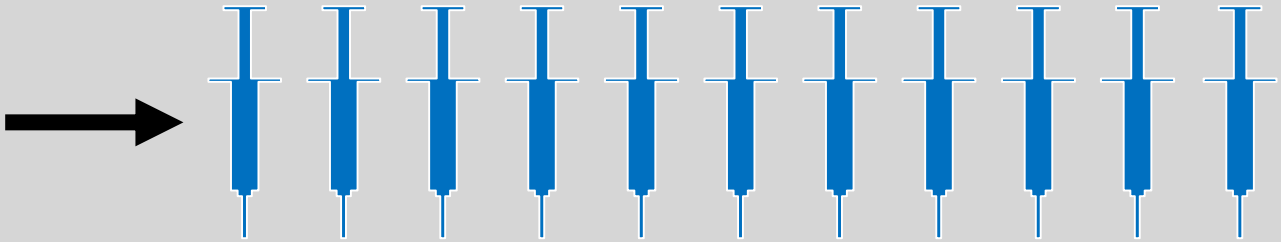
Short GCSF vs long GCSF: differenze cliniche

Short-acting G-CSFs

Filgrastim (standard G-CSF)

Lenograstim (glycosylated G-CSF)

Dosi giornaliere



Long-acting G-CSFs

Lipegfilgrastim (glycoPEGylated G-CSF)

Pegfilgrastim (PEGylated G-CSF)

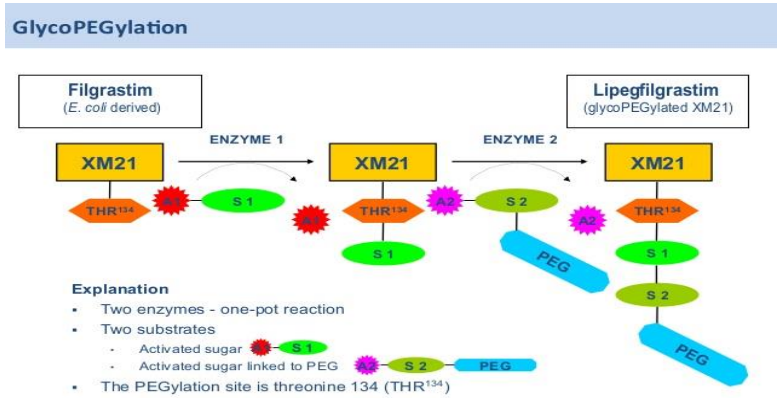
Una dose per ciclo di chemioterapia

Sistema Socio Sanitario Regione Lombardia ASST Bergamo Ovest

Oncologia Medica Treviglio

1. Smith TJ, et al. *J Clin Oncol.* 2006;24:3187-3205;
2. 2. EMEA: http://www.ema.europa.eu. Accessed October 2014.

Forme peghilate: lipopegfilgrastim



Phase III study, XM22-03

Conclusions :

- **Non inferiority of lipegfilgrastim 6 mg vs pegfilgrastim 6 mg demonstrated on DSN in cycle 1**
- Secondary endpoints : significant differences in favor of lipegfilgrastim on following endpoints :
  - **Lower incidence of severe neutropenia in cycle 2**
  - **Lower depth of neutropenia in cycles 2 and 3**
  - **Time to ANC recovery ≥ 2 x10^9/L shorter in cycles 1, 2 and 3**
- **Comparable safety profiles**

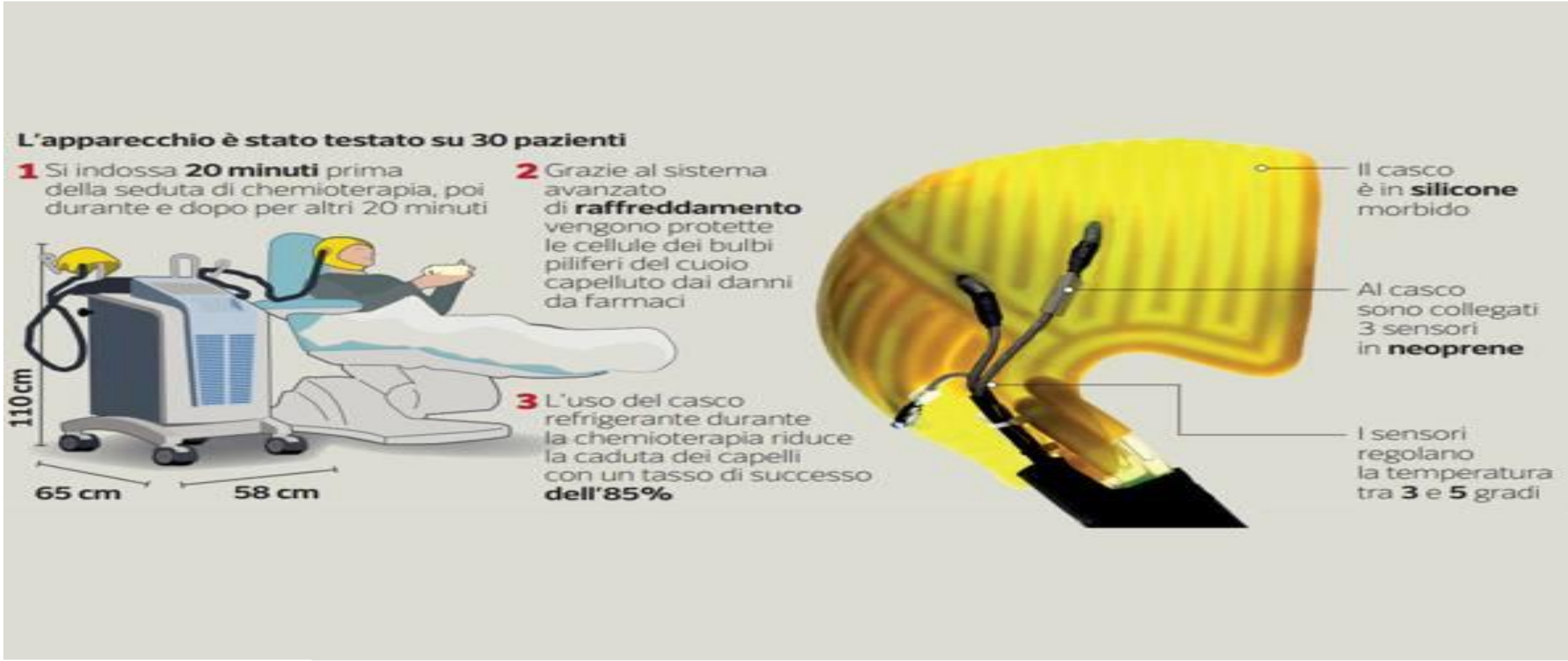
Meta-analisi:
Confornto Lipopeg vs peg vs filg

	Lipeg vs peg	Lipeg vs filgrastim
Neutropenia severa al primo ciclo (RR)	0.80 (95% IC: 0.63 -1.03)	0.79 (95% IC: 0.61 – 1.03)
Neutropenia severa cicli successivi (RR)	0.53 (95% IC: 0.35 – 0.79)	0.45 (95% IC 0.27- 0.75)
Tempo di recupero ANC	-1.75 (95% IC: -2.61 , -0.90)	-1.88 (95% IC: -2.82, -0.95)

RR: rischio relativo

Bond et all. Value in healt. 2015 PCN26

Alopecia


L'apparecchio è stato testato su 30 pazienti
1 Si indossa 20 minuti prima della seduta di chemioterapia, poi durante e dopo per altri 20 minuti
110 cm
65 cm
58 cm
2 Grazie al sistema avanzato di raffreddamento vengono protette le cellule dei bulbi piliferi del cuoio capelluto dai danni da farmaci
3 L'uso del casco refrigerante durante la chemioterapia riduce la caduta dei capelli con un tasso di successo dell'85%
Il casco è in silicone morbido
Al casco sono collegati 3 sensori in neoprene
I sensori regolano la temperatura tra 3 e 5 gradi

Alopecia: casco refrigerato

JAMA | Original Investigation

Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer
The SCALP Randomized Clinical Trial

Julie Nangia, MD; Tao Wang, PhD; Cynthia Osborne, MD; Polly Niravath, MD; Kristen Otte, BA; Steven Papish, MD; Frankie Holmes, MD; Jame Abraham, MD; Mario Lacouture, MD; Jay Courtright, MD; Richard Paxman, BSc; Mari Rude, ANP; Susan Hilsenbeck, PhD; C. Kent Osborne, MD; Mothaffar Rimawi, MD

	Cooling (n = 95)		Noncooling (n = 47)	
Parameter	No.	% (95% CI)	No.	% (95% CI)
Hair preservation[b]				
Success[c]	48	50.5 (40.7-60.4)	0	0 (0-7.6)
Alopecia grade 0	5	5.3		
Alopecia grade 1	43	45.3		
Failure	47	49.5 (39.6-59.4)	47	100 (92.4-100)

Esperienza Oncologia Brindisi

ALOPECIA/HL	G0	G1	G2	G3	G4
n (%)	6 (15%)	15 (37.5%)	7 (17.5%)	10 (25%)	2 (5%)

Tab 1: A/HL according to the Dean's scale

70% delle pazienti no necessità parrucca

Cortesia del dr. Cinieri S; Oncologia Brindisi; Senatore Antonio Perrino Hospital

Casco refrigerato: meta-analisi

Study or Subgroup	Scalp cooling Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelstyn 1977	20	40	30	37	23.8%	0.62 [0.44, 0.87]
Giaccone 1988	11	19	15	16	12.4%	0.62 [0.41, 0.92]
MacDuff 2003	5	7	10	10	6.7%	0.72 [0.44, 1.17]
Nangia 2017	47	95	47	47	48.3%	0.50 [0.41, 0.61]
Satterwhite 1984	3	12	12	13	8.8%	0.27 [0.10, 0.73]
Total (95% CI)		**173**		**123**	**100.0%**	**0.54 [0.46, 0.63]**
Total events	86		114			

Heterogeneity: Chi² = 4.78, df = 4 (P = 0.31); I² = 16%
Test for overall effect: Z = 7.70 (P < 0.00001)

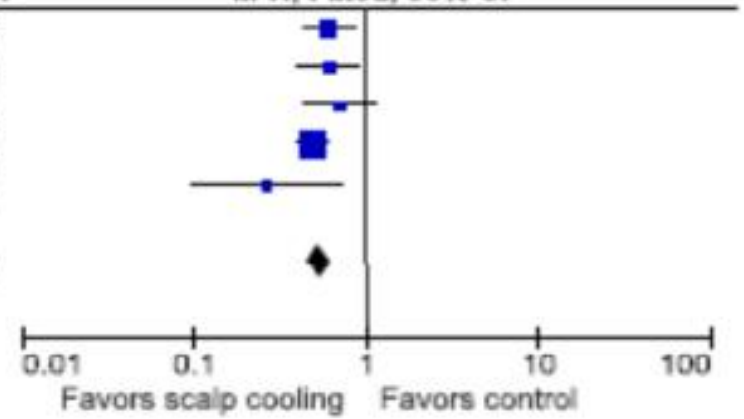


Figure 4: Forest Plot – Significant Alopecia

Rugo et al; Clin Breast Cancer 2017

Conclusioni

- La terapia di supporto/ancillare fa parte integrante del trattamento chemioterapico
- Nausea e vomito oggi vengono controllati in >90% dei pazienti
- L'uso corretto di ESA e ferro permettono di ridurre la necessità di trasfusioni del 50%
- Obbligatorio un uso piu' oculato del sangue!
- I fattori di crescita della serie bianca riducono infezioni e mortalità, permettono l'uso di schemi piu' intensivi (es. dose dense)
- L'uso di farmaci biosimilari per la terapia di supporto riduce i costi
- La prevenzione dell'alopecia potrebbe non essere piu un tabù..