Erythropoiesis stimulating agent is Contraindicated in Cancer Patients

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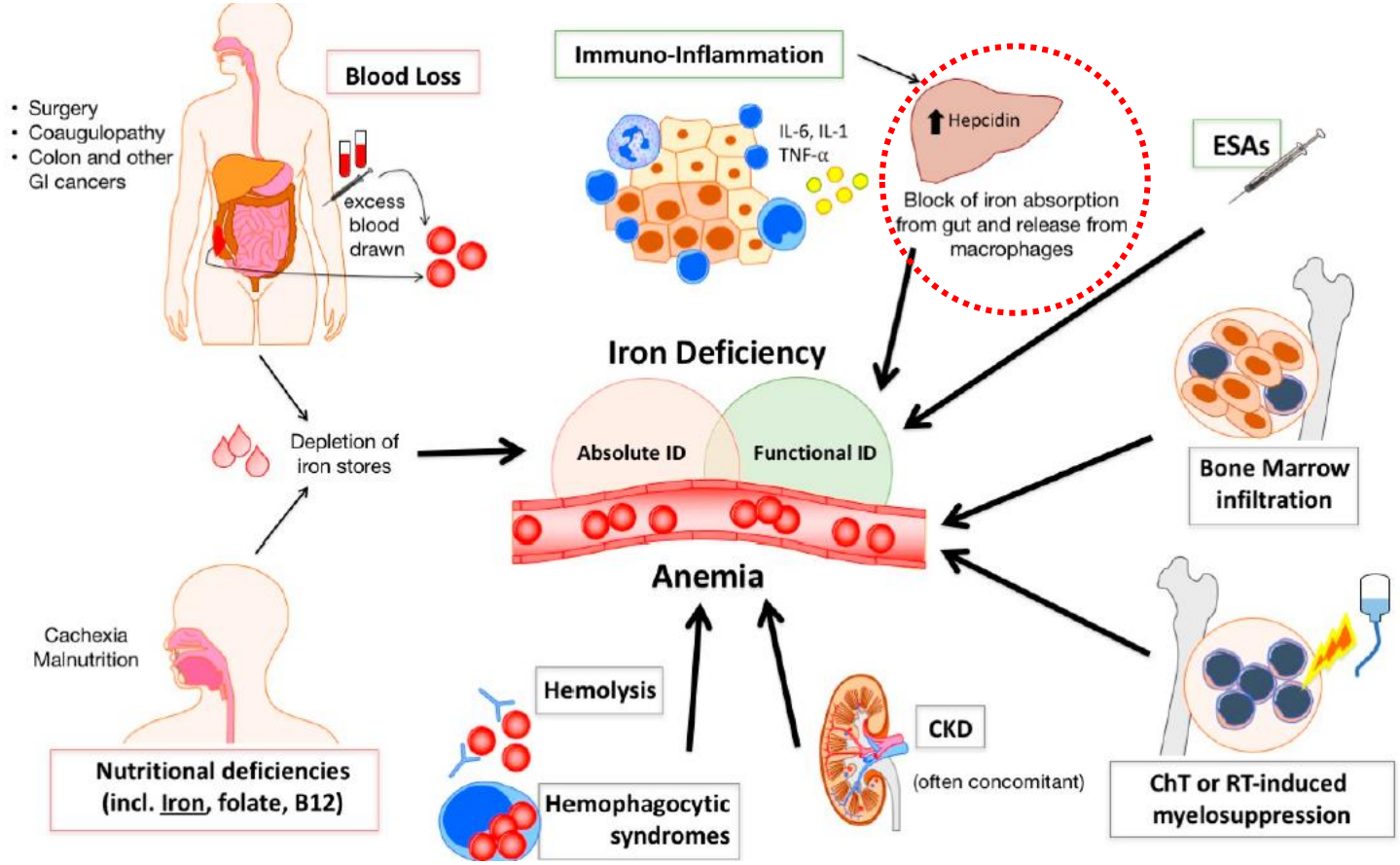
Introduction: Anemia

- One of the most common complications among cancer patients, affecting up to 90% depending on the type of malignancy and treatment intensity
- It results from multiple causes, including chemotherapy-induced myelosuppression, chronic inflammation, nutritional deficiency, and renal dysfunction
- Significantly contributes to fatigue, decreased performance status, and lower quality of life, often leading to treatment interruptions

Cancer-Related Anemia	Treatment-Related Anemia	Patient-Related Anemia
• Blood loss • Hemolysis • Tumor infiltration and degradation of the bone marrow • Inflammation-associated anemia	• Surgery-related blood loss • Radiotherapy-induced bone marrow suppression • Chemotherapy-induced hematopoiesis suppression • Chemotherapy-induced nephrotoxicity	• Poor appetite • Nutritional deficiency

Multifactorial pathogenesis of cancer-related anemia

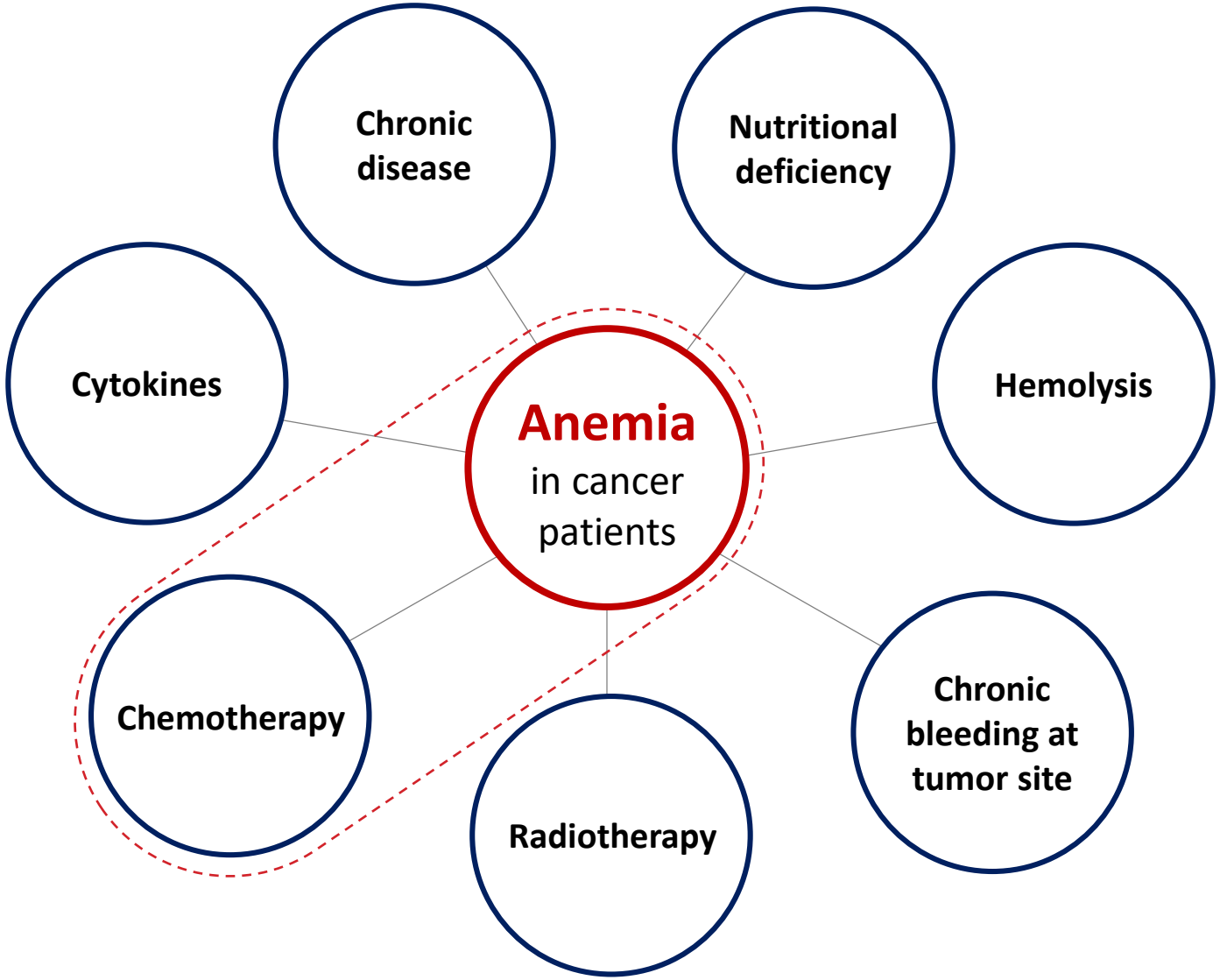
- ID in cancer patients can be due to multiple concurring mechanisms, including bleeding (e.g., in gastr ointestinal cancers or after surgery), malnutrition, medications, and hepcidin-driven iron sequestratio n into macrophages with subsequent iron-restricted erythropoiesis



ID, Iron Deficiency; ChT, Chemotherapy; RT, Radiotherapy;
ESA, Erythropoietic Stimulating Agents; CKD, Chronic Kidney Disease

Busti F. et al. Pharmaceuticals (Basel). 2018 Sep 30;11(4):94.

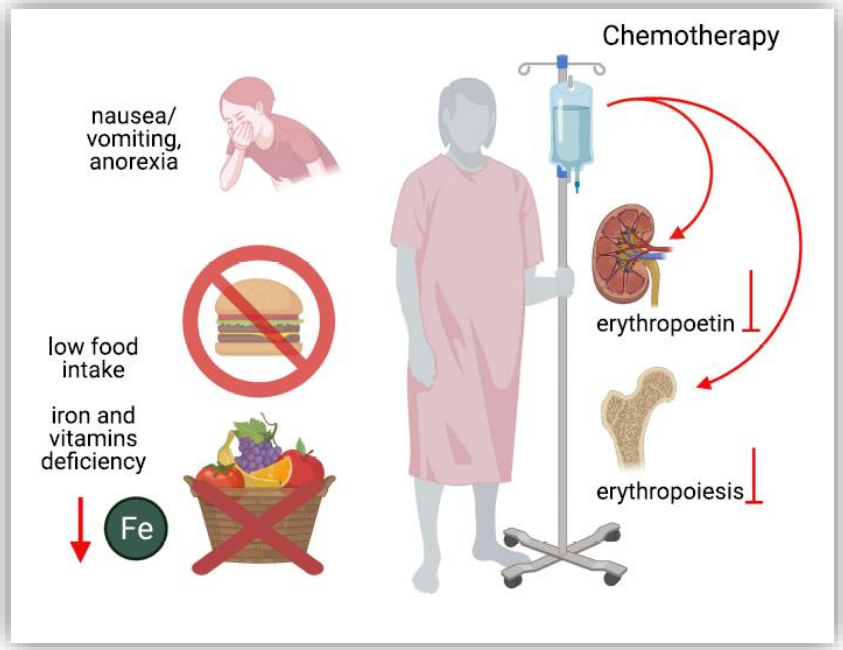
What is chemotherapy-induced anemia (CIA) ?



Pathogenesis of chemotherapy-induced anemia

- Chemotherapy-induced anemia is related to the toxic effect of anticancer treatments on bone marrow or to a nephrotoxic effect, which negatively influence EPO production. [1,2]
  - the condition is often induced by platinum-based regimens. Indeed, beyond the direct toxic effect on erythropoiesis, platinum-based chemotherapy may cause nephrotoxicity with a subsequent drop in EPO production.[1]

- **Anticancer treatments can induce gastro-enteric side effects, such as anorexia, nausea, and vomiting, and diarrhea[1]**
  - These side effects objectively decrease food intake or lead to a loss of nutrients, vitamins, and minerals, ultimately affecting erythropoiesis



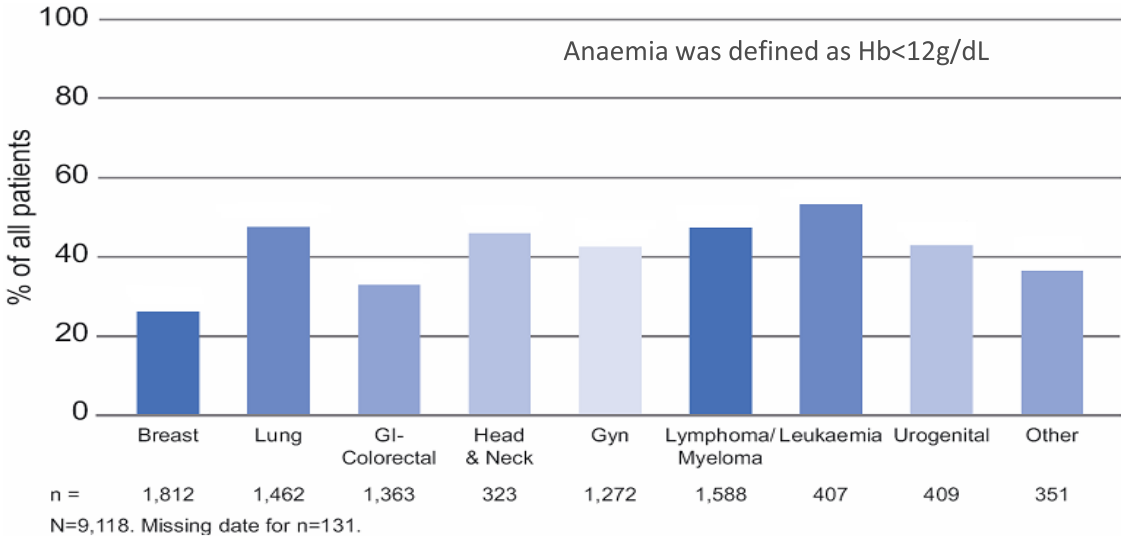
CIA is often precipitated by platinum-based therapies.[20] Factors that are associated with the development of platinum-induced anemia include early decrease in hemoglobin following treatment, cumulative platinum dose, advanced age, failure to respond to chemotherapy, and high concentration of residual platinum in the bloodstream following administration.[16,21] Mechanisms of CIA by platinum-based regimens involve direct suppression of erythroid progenitor cells within the bone marrow as well as nephrotoxic effects on erythropoietin-producing cells within the kidney.[22,23] States of inherent erythropoietin deficiency secondary to cisplatin-induced renal tubular damage can be prevented or treated by replacement with recombinant hormone.[24] Nonplatinum-based chemotherapy regimens, including antimicrotubular agents, campothecins, and biologics, can also be particularly myelosuppressive.[25,26]

1. Madeddu C et al. J Exp Pharmacol. 2021 Jun 24;13:593-611.
2. Bryer and Henry. International Journal of Clinical Transfusion Medicine 2018:6 21–31

Prevalence of anemia in cancer

- Anemia occurred more than 30% of cancer patients at diagnosis before the initiation of antineoplastic therapy, rising to 67% once treatment is initiated.
- CIA (Cancer-and-chemotherapy induced anemia) prevalence differs among cancer types, with the highest percentage of anemic patients reported in lung cancer, gynecologic or genitourinary, and gastrointestinal tumors

[Anaemia prevalence in different cancer types]



[Incidence of anemia in patients receiving chemotherapy]

Table 2 Proportion of patients developing CIA by CIA severity and type

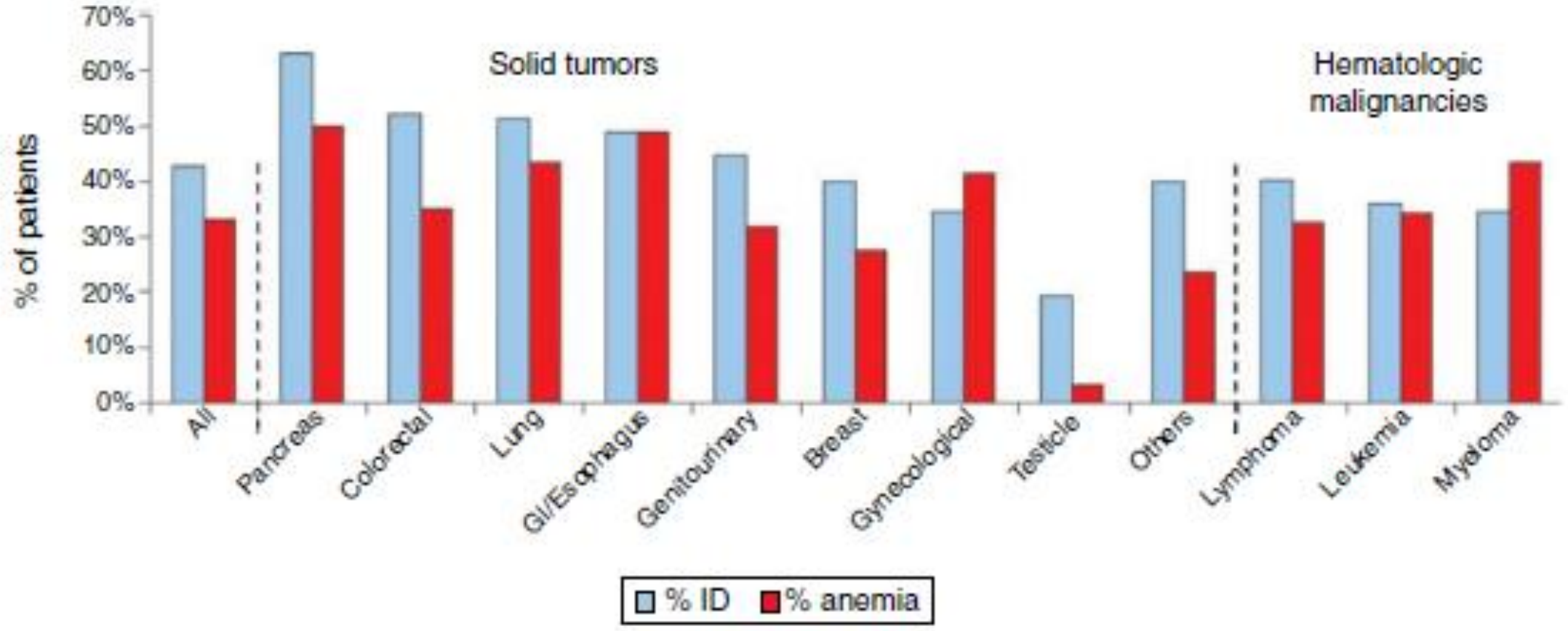
	Total (N=4,426)	Breast (N=2,348)	Colorectal (N=678)	Gastric (N=193)	Lung (N=888)	Ovary (N=319)
Incidence proportion (%, 95% confidence interval)						
Anemia, any grade	89.5 (88.6–90.4)	86.3 (84.9–87.7)	91.7 (89.7–93.8)	98.4 (96.7–100)	93.1 (91.5–94.8)	93.1 (90.3–95.9)
Percentage of CIA[a]						
Anemia severity[a]						
Grade 1	57.8	61.0	71.4	41.1	51.3	36.4
Grade 2	33.7	33.3	24.1	44.7	35.3	45.5
Grade 3	7.6	5.3	4.2	11.1	12.0	16.2
Grade 4	0.9	0.4	0.3	3.2	1.5	2.0
Anemia type[a]						
Microcytic	5.3	4.0	11.4	7.4	4.0	3.1
Normocytic	84.9	89.3	75.9	76.7	84.6	79.6
Macrocytic	9.8	6.7	12.7	15.9	11.4	17.3
Anemia type[a]						
Hypochromic	8.7	7.1	16.6	10.1	7.5	5.4
Normochromic	46.9	50.7	41.8	48.1	42.8	42.5
Hyperchromic	44.4	42.2	41.6	41.8	49.8	52.0

Note: [a]Using the most severe CIA episode for patients with multiple CIA episodes.
Abbreviation: CIA, chemotherapy-induced anemia.

Kristof Verraes et al., Annals of Gastroenterology 2015;28, 19-24; Ludwig H, 2004; Ludwig et al. Annals of Oncology. 2013 May 29; Hairong Xu et al., Clinical Epidemiology 2016:8 61–71

Prevalence of iron deficiency and anemia in cancer patients

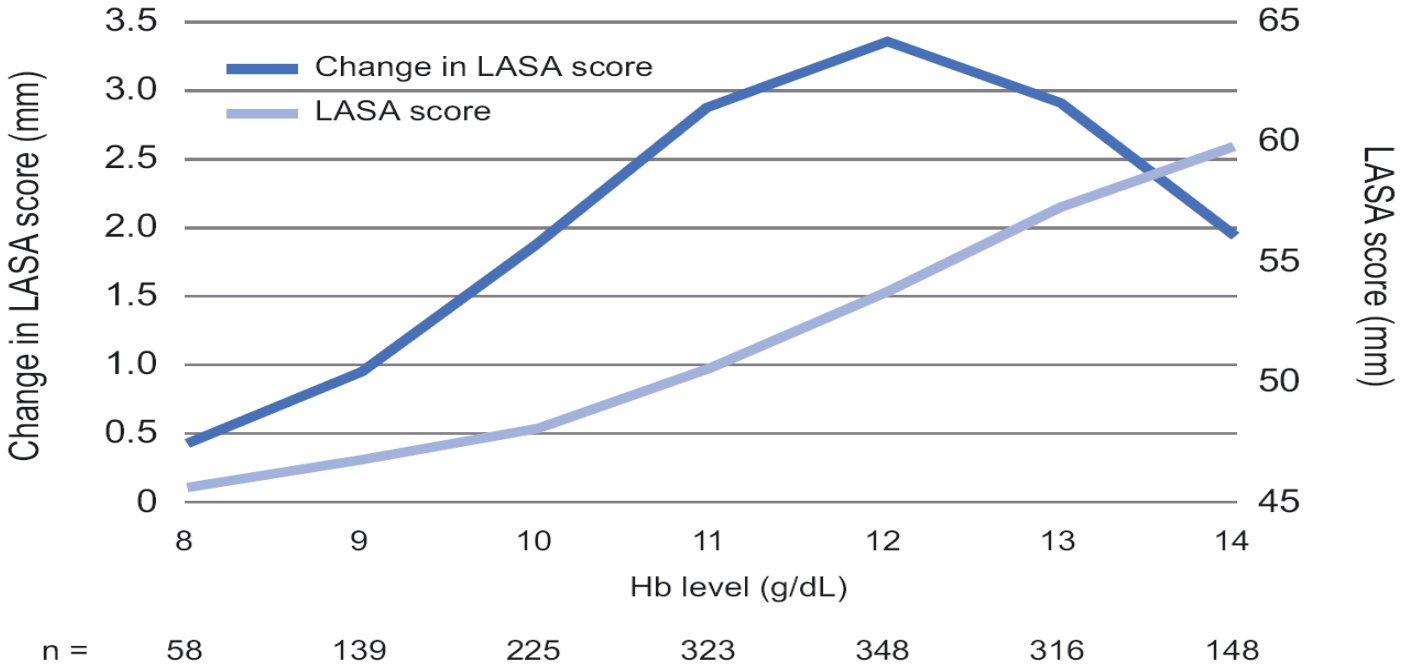
A high prevalence of iron deficiency across different tumor types and iron deficiency correlated with anemia.



Ludwig et al. Annals of Oncology. 2013 May 29

There is direct relationship between Hb levels and Quality of Life(QoL)

- Longitudinal and incremental analysis of the correlation between Hb levels and Quality of Life in cancer patients receiving chemotherapy
- Direct relationship between Hb levels increases and corresponding QoL improvements in cancer patients receiving chemotherapy across the clinically relevant Hb range of 8-14g/dL



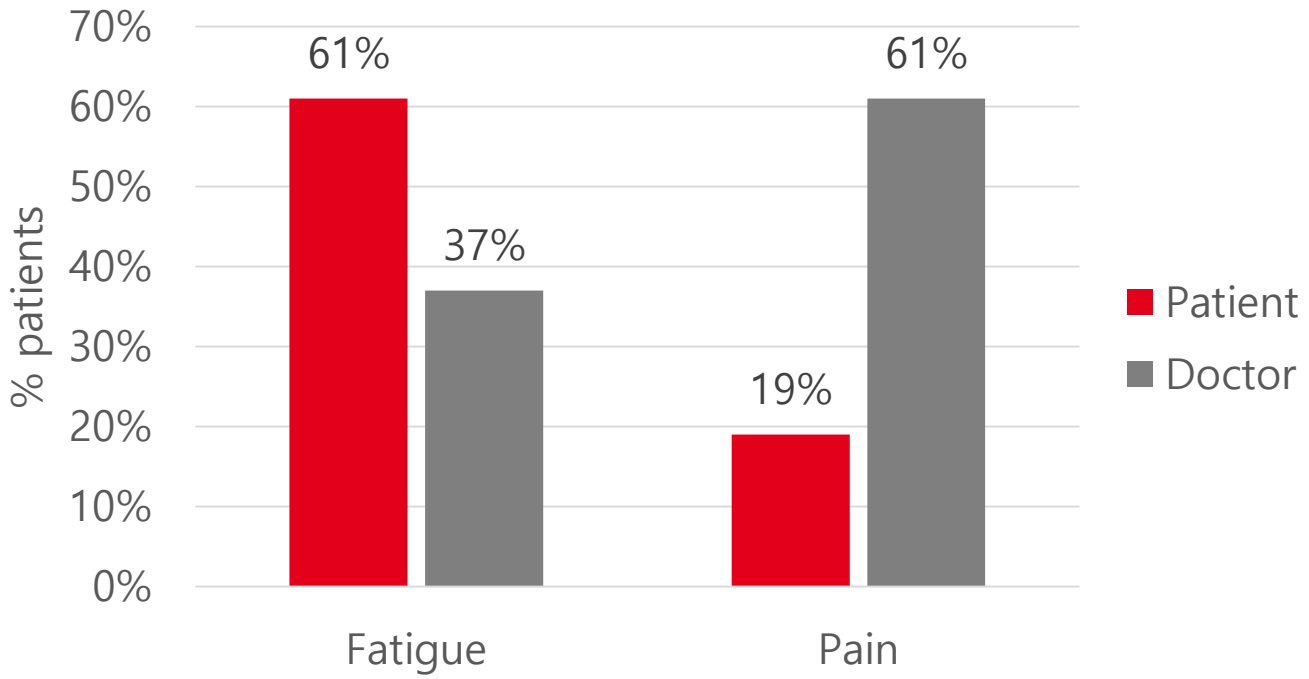
The maximal incremental gain in QoL occurs when Hb is in the range of 11 to 13 g/dL

LASA, Linear Analog Scale Assessment

Crawford J et al. Cancer. 2002 Aug 15;95(4):888-95.

Fatigue has a greater impact on cancer patients' lives than pain

- Responses to the question:
  which symptom do you think affects/affected your everyday life more, pain or fatigue?
- Although oncologists believed that pain adversely affected their patients to a greater degree than fatigue (61% v 37%), patients felt that fatigue adversely affected their daily lives more than pain (61% v 19%)



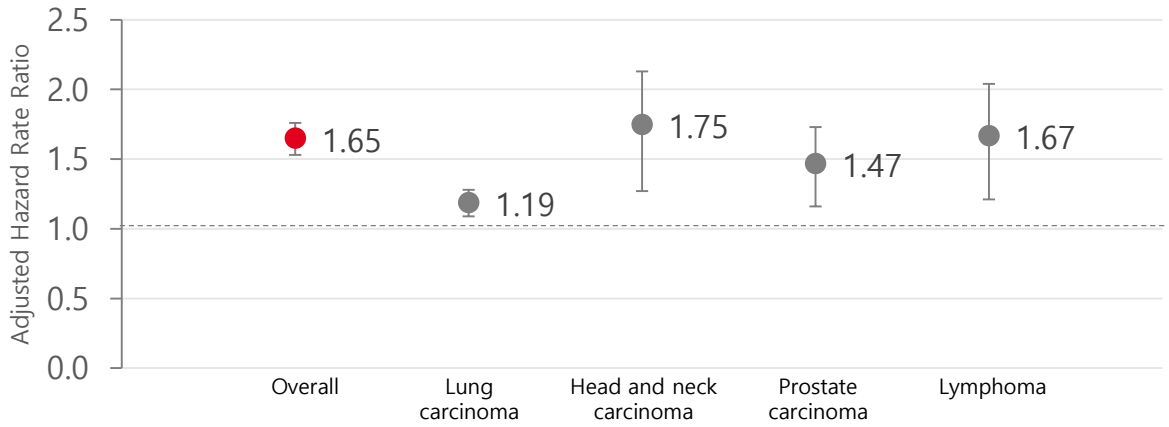
A survey was designed to characterize the epidemiology of cancer-related fatigue from the perspectives of the patient, primary caregiver, and oncologist. A telephone survey included 419 cancer patients recruited. More than three quarters of patients (78%) experienced fatigue (defined as a general feeling of debilitating tiredness or loss of energy) during the course of their disease and treatment.

Vogelzang NJ, Semin Hematol. 1997 Jul;34(3 Suppl 2):4-12.

Anemia is associated with shorter survival times for cancer patients

- Consequences of anemia may include impaired response to cancer treatment and reduced overall survival (OS)[1]
- There was a 65% overall increase in the risk of mortality in cancer patients with anemia compared with those without anemia[2,3]
- The impact of anemia on survival has been related to delay in initiating, or failure to complete, the ChT regimens[2]

Relative risk of death in anemic patients with cancer[3]



Modified from Ref 2. Caro(2001)

Comprehensive literature review. 60 papers that reported the survival of cancer patients according to either hemoglobin levels or the presence of anemia were included. Among these papers, 25% related to patients with lung carcinoma, 17% related to patients with head and neck carcinoma, 12% related to patients with multiple myeloma, 10% related to patients with prostate carcinoma, 8% related to patients with cervicouterine carcinoma, 7% related to patients with leukemia, 5% related to patients with lymphoma, and 16% related to patients with other types of malignancies. Anemia is associated with shorter survival times for patients with lung carcinoma, cervicouterine carcinoma, head and neck carcinoma, prostate carcinoma, lymphoma, and multiple myeloma

1. Aapro M, et al. Ann Oncol 2018;29(Suppl 4):iv96–iv110. (ESMO guidelines)
2. Busti F. et al. Pharmaceuticals (Basel). 2018 Sep 30;11(4):94.
3. Caro JJ. et al. Cancer. 2001 Jun 15;91(12):2214-21

Clinical relevance of CIA

- Anaemia and iron deficiency (ID) are frequent complications in patients with solid tumours or haematological malignancies, particularly in patients treated with chemotherapeutic agents.

  Frequently, anaemia is associated with fatigue, impaired physical function and reduced quality of life (QoL).

Chemotherapy response ↓

Quality Of Life ↓

Poor survival

ESMO

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*

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*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: October 2017.

Anaemia and iron deficiency (ID) are frequent complications in patients with solid tumours or haematological malignancies, particularly in patients treated with chemotherapeutic agents [1–3]. Frequently, anaemia is associated with fatigue, impaired physical function and reduced quality of life (QoL) [4–7]. Consequences of anaemia may include impaired response to cancer treatment and reduced overall survival (OS), even though a causal direct relationship has not yet been established [8, 9].

These new ESMO Clinical Practice Guidelines provide tools to evaluate anaemia, also in patients with myelodysplastic syndromes (MDS), and include recommendations on how to safely manage chemotherapy-induced anaemia (CIA) with intravenous (i.v.) or oral administration, red blood cell (RBC) transfusions and combinations of these treatments [10–13]. 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. Underlying causes of anaemia, mainly impaired erythropoietic activity and disturbed iron homeostasis, can be consequences of increased release of inflammatory cytokines due to the underlying cancer and/or toxicity of cancer therapy. Furthermore, vitamin B12 and folate deficiency are relatively rare causes of anaemia in cancer patients.

Notably, also more than half of patients with MDS are characterised by a haemoglobin (Hb) level < 10 g/dL, resulting in reduced functional capacities and health-related QoL, and > 80% of these patients require RBC transfusions [14–17]. However, ESAs were not approved by the European Medicines Agency (EMA) for use in MDS patients despite being used effectively in MDS for at least 20 years; their activity has been demonstrated in numerous clinical trials, with published evidence existing for more than 2500 ESA-treated MDS patients [14]. Randomised clinical trials are ongoing.

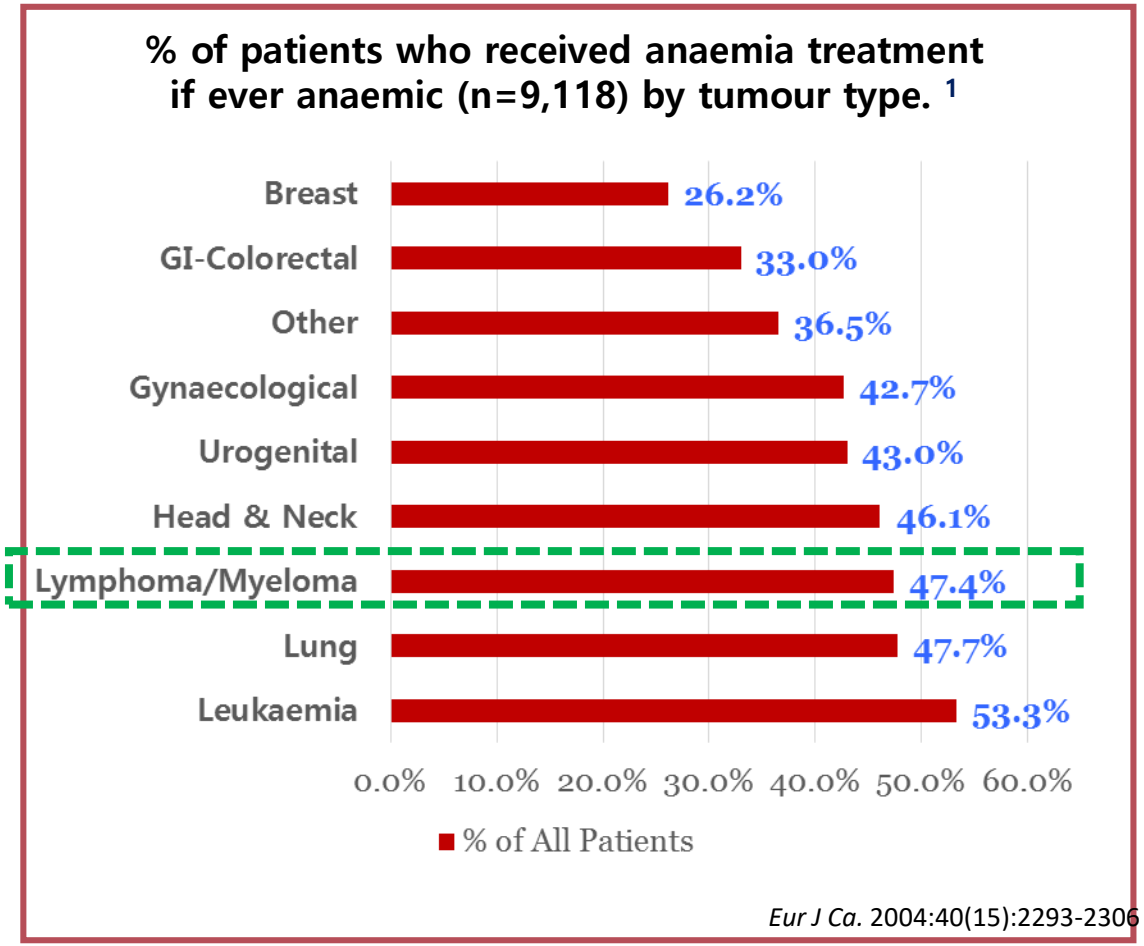
Since the publication of the European Society of Medical Oncology (ESMO) anaemia Clinical Practice Guidelines in 2010 [18] and the last review of the European Organisation for Research and Treatment of Cancer (EORTC) anaemia treatment guidelines in 2006 [19] (last update in 2007 [20]), clinical experience with ESAs and iron preparations and the understanding of iron homeostasis have markedly increased [10, 21]. Furthermore, specific safety aspects of the different treatment options have been addressed by several analyses and reviews in recent years, although data on the use of blood transfusions in cancer patients are sparse. Therefore, new ESMO guidelines for the diagnosis and treatment of anaemia and ID in cancer patients were deemed necessary. In addition, these guidelines include aspects related to anaemia management in patients with MDS and update the most recent ESMO and European LeukemiaNet (ELN) treatment guidelines for MDS [15, 22].

Questions addressed by these guidelines and respective recommendations including levels of evidence and grades of recommendations [23] are summarised in Table 1 for the management

Aapro M, et al. Ann Oncol 2018;29(Suppl 4):iv96–iv110. (ESMO guidelines)

% of treatment of CAA

- ✓ 31.7% of patients who were not receiving cancer treatment at enrollment were anemic.
- ✓ Anemia patients with **Breast cancer** were least likely to receive anemia treatment (73.8%)



Eur J Ca. 2004:40(15):2293-2306

Table. Higher relative risk for death in anemic patients [2]

Tumor type	Relative risk for death in anemic patients	
	%	(95% Confidence interval)
Lung carcinomas	19%	(10%–29%)
Head and neck carcinomas	75%	(37%–123%)
Prostate cancer	47%	(21%–78%)
Lymphoma	67%	(30%–113%)
Overall estimated higher risk for death	65%	(54%–77%)

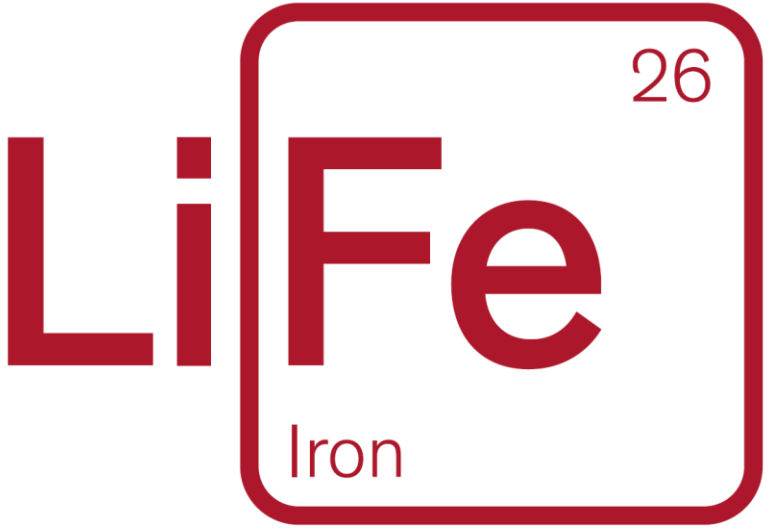
Ref. 1.Ludwig H. et al.,. *1. Eur J Ca*. 2004:40(15):2293-2306, 2. Caro JJ et al. *Cancer* 2001;91:2214–2221

Recommendation for management of CIA

Red blood cell transfusion

EPO stimulating agents

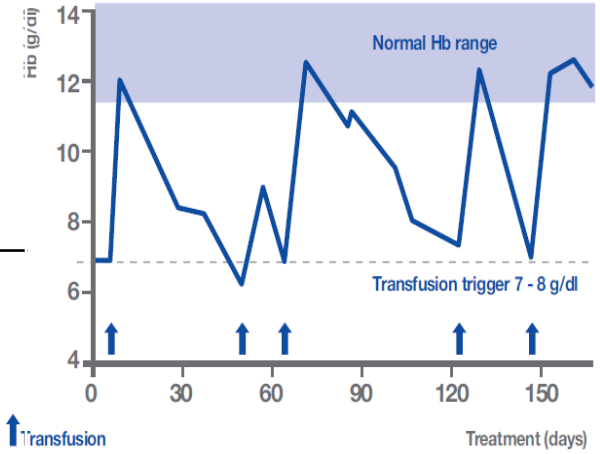
Iron supplementation



- ✓ For patients receiving chemotherapy, *the increasing hemoglobin level* is of great importance for improving survival and anti-tumor efficacy of chemotherapy.
- ✓ If anemia is not due to absolute or functional iron deficiency, there are currently **only two proven methods, *ESA and RBC transfusion.***

Risk & goals of ESA vs. RBC transfusion

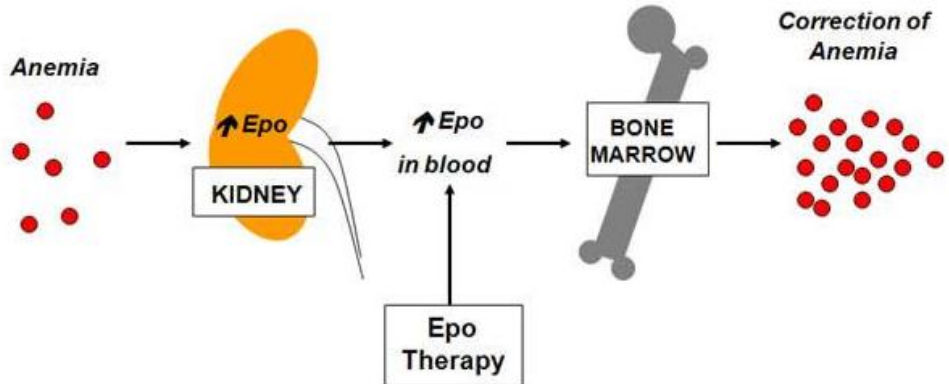
ESA in the cancer setting		**RBC Transfusion**
• **Transfusion avoidance** • **Gradual improvement in anemia-related symptoms**	**Benefits**	• Rapid increase of Hb and hematocrit levels • Rapid improvement in anemia-related symptoms
• Increased thrombotic events • Possible decreased survival • Time to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



Mechanism of action

- ESAs are synthetic forms of erythropoietin, such as epoetin alfa or darbepoetin alfa, designed to stimulate red blood cell production
- They bind to erythropoietin receptors on bone-marrow progenitor cells, promoting proliferation and differentiation of erythroid lineages
- This stimulation leads to a gradual rise in hemoglobin levels and improved oxygen-carrying capacity of the blood

→ ***By mimicking the natural hormone, ESAs restore the body's ability to produce red cells suppressed by chemotherapy***



Benefit of ESA therapy

- ESAs significantly reduce the need for red blood cell transfusions, which carry risks of infection and alloimmunization
- A gradual hemoglobin rise of about 1 g/dL every 2–4 weeks can be expected with appropriate dosing
- Many patients report improvement in fatigue and general well-being, contributing to a better quality of life
- Their outpatient use provides a convenient and non-invasive approach to managing chronic chemotherapy-related anemia

→ *The primary goal is to alleviate fatigue and reduce transfusion burden in long-term care*

Risk of ESA therapy

- ***Possible increased mortality and tumor progression***
- ***Thromboembolism***
- ***Hypertension***
- ***Pure red cell aplasia (PRCA)***

Risk of ESA therapy in cancer setting

Possible increased mortality and tumor progression

- In the late 2000s, the safety of ESAs was discussed when meta-analyses suggested that ***ESA treatment may affect mortality in cancer patients***

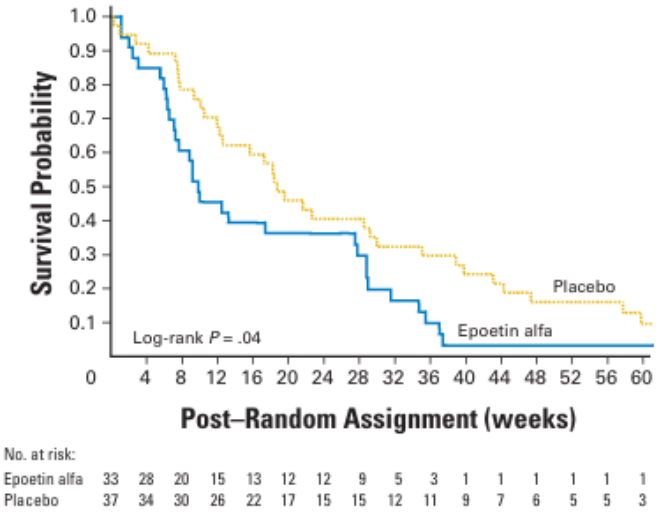
- The use of ESAs was related to an adverse impact on survival in certain tumor entities (e.g., non-small-cell lung cancer [NSCLC], head and neck cancer receiving radiotherapy, cervical cancer receiving chemoradiotherapy, and metastatic breast cancer receiving chemotherapy), as shown by several controlled trials

Risk of ESA therapy in cancer setting

Possible increased mortality and tumor progression

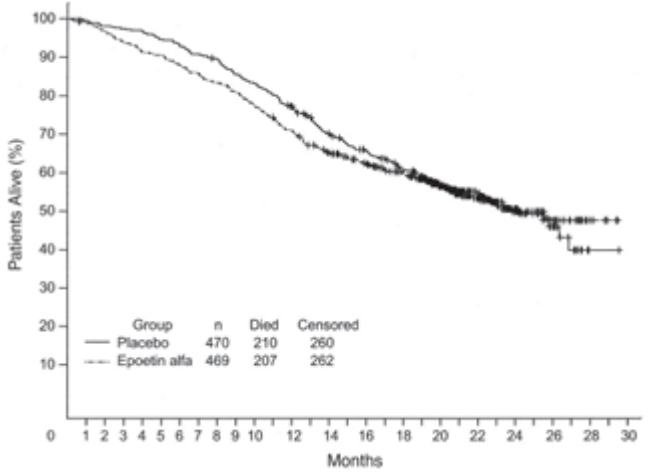
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non–Small-Cell Lung Cancer With Disease-Related Anemia



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

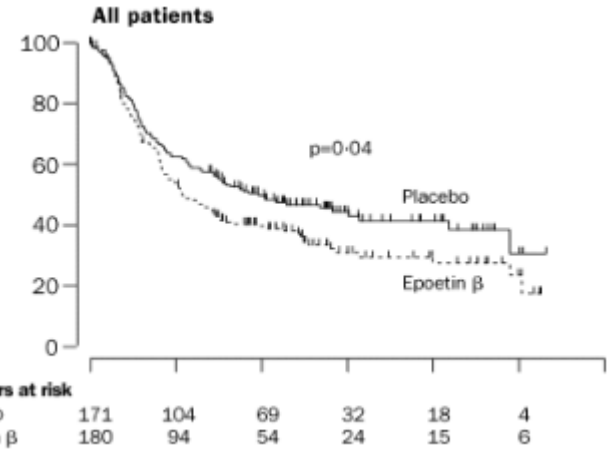
Maintaining Normal Hemoglobin Levels With Epoetin Alfa in Mainly Nonanemic Patients With Metastatic Breast Cancer Receiving First-Line Chemotherapy: A Survival Study



ELSEVIER
The Lancet
Volume 362, Issue 9392, 18 October 2003, Pages 1255-1260
THE LANCET

Articles

Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial



NSCLC unsuitable for curative therapy and baseline Hgb levels < 12 g/dL

Risk of ESA therapy in cancer setting

Possible increased mortality and tumor progression

- In the late 2000s, the safety of ESAs was discussed when meta-analyses suggested that ***ESA treatment may affect mortality in cancer patients***
- Some reports suggested a potential role of the EPO receptor (EpoR) on tumour cells in tumour progression, yet there has been a controversial discussion

- The use of ESAs was related to an adverse impact on survival in certain tumor entities (e.g., non-small-cell lung cancer [NSCLC], head and neck cancer receiving radiotherapy, cervical cancer receiving chemoradiotherapy, and metastatic breast cancer receiving chemotherapy), as shown by several controlled trials
- Recent Cochrane review included subgroup analyses and showed ***statistically significant on-study mortality in patients with baseline Hb>12 g/dL*** but not for Hb categories Hb<10 g/dL and Hb¼10–12 g/dL that correspond to the currently approved cut-off for initiation and the target Hb range of ESA therapy

Risk of ESA therapy in cancer setting

Thromboembolism

- The cause of VTE in patients with cancer is complex
- Increased thromboembolic event including VTE are associated with ESA therapy in cancer patients

JAMA

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

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

Risk of ESA therapy in cancer setting

Thromboembolism

- Additionally, an increased risk of stroke was associated with darbepoietin alfa in a clinical trial of patients with CKD

- Increased thromboembolic event including VTE are associated with ESA therapy in cancer patients → approximately 1.5 to 1.7 times higher than in control
- Patients with risk factors (prior history of VTE, hypercoagulability, prolonged immbolization, etc) may be more susceptible to thrombosis with EAS use
- In the absence of prospective randomised studies showing that antithrombotic therapy reduces the risk of VTEs in ESA-treated patients, prophylactic antithrombotic treatment is not recommended

Risk of ESA therapy in cancer setting

Hypertension

- Cochrane review: increased risk for hypertension with ESA use in patients with cancer
- Blood pressure should be controlled and be monitored regularly throughout treatment

PRCA

- Cases of PRCA related to anti-EPO antibodies have been reported rarely
- Should be suspected whenever a response to rEPO is lost

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update

Recommendations

Clinical question 1

To reduce the need for RBC transfusions, should ESAs be offered to patients who have chemotherapy-associated anemia?

Recommendation 1.1. Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin (HgB) has declined to < 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 2

To reduce the need for RBC transfusions, should ESAs be offered to anemic patients with cancer who are not receiving concurrent myelosuppressive chemotherapy?

Recommendation 2.1. ESAs should not be offered to most patients with nonchemotherapy-associated anemia (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 2.2. ESAs may be offered to patients with lower risk myelodysplastic syndromes and a serum erythropoietin level ≤ 500 IU/L (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update

Clinical question 3

What special considerations apply to adult patients with nonmyeloid hematologic malignancies who are receiving concurrent myelosuppressive chemotherapy?

Recommendation 3. In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA. Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where risk of thromboembolic complications is increased (see Recommendations 4 and 6). In all cases, blood transfusion is a treatment option that should be considered (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Clinical question 4

What examinations and diagnostic tests should be performed before making a decision about using an ESA to identify patients who are likely to benefit from an ESA?

Recommendation 4. Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy. Such causes should be appropriately addressed before considering the use of ESAs. Suggested baseline investigations are listed in Table 1 (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical question 6

Do ESAs increase the risk of thromboembolism?

Recommendation 6. ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Current guideline recommendation

- Initiate ESA only for chemotherapy-induced anemia when Hb < 10 g/dL and symptoms are present
- Target Hb ≤ 12 g/dL and use the lowest effective dose to avoid transfusion
- No recommendation for patients with cancer-related anemia in the absence of chemotherapy
- No recommendation for patients undergoing chemotherapy in curative intention
- Discontinue treatment once chemotherapy ends of if there is no adequate response after 6-8 weeks
- Evaluate and correct iron deficiency before or during ESA therapy
- Individual risk for thromboembolism must be evaluated and considered
- Discuss potential benefits and risk thoroughly with patients before initiation

→ ***Highlighting careful patient selection and shared decision-making***

Summary

- ESAs effectively reduce transfusion needs in chemotherapy-induced anemia but should be used with caution.
- Several randomized clinical trials have demonstrated that the use of ESAs is accompanied by serious side effects, such as an increase in thromboembolic events, mortality, and inferior outcomes.
- Clinicians must be aware of these issues and should carefully weigh the risks of ESAs against transfusion risks.

→ ***ESAs remain a valuable but double-edged tool—effective only when used precisely***

Thanks for your attention