Erythropoiesis stimulationg agents:

evidence for their use for the treatment of anemia in thoracic tumors and MICU

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14th Oct 2011

Anemia and cancer

- Common hematological abnormality
- Incidence and degree of anemia depend on
  - type and stage of the malignant disease
  - regimen and intensity of treatment
  - outcome of complications, such as intercurrent infections or surgeries
- Estimates of the prevalence and incidence of anemia vary according to
  - population characteristics
  - tumor type and stage
  - nature and intensity of the treatment

Burden of anemia in cancer

- An epidemiological survey of the Canadian cancer population showed that 28% of cancer patients were anemic at some stage in the course of the disease and that 12% of these patients needed blood transfusions

Cancer Prev Control 1999;3:207–12

- Coiffier B et al showed 37% of cases with colorectal, breast, lung or ovarian cancer, Hodgkin's disease or non-Hodgkin's lymphoma undergoing non-platinum-based chemotherapy developing anaemia

Eur J Cancer 2001;37:1617–23

European Cancer Anaemia Survey (ECAS)

- Prospective epidemiological survey conducted in 24 European countries
  - Prevalence of anaemia at enrolment was 39.3%
  - Percentage of patients who were anaemic at least once during the survey was greater than 50% for all tumour types.
  - Incidence of anaemia during cancer treatment was 53.7%
  - Higher in patients who received chemotherapy than in those who received concomitant chemoradiotherapy (41.9%) or radiotherapy alone (19.5%)
- Hematological malignancies>> lung and breast/gynaecological malignancies >> gastrointestinal cancer

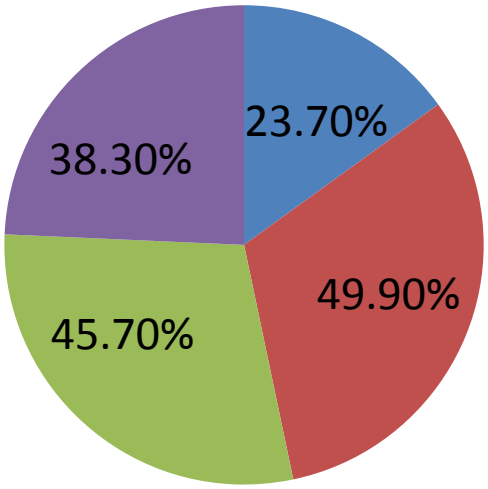
Eur J Cancer 2004;40:2293–306

Anemia in Lung Cancer

- Cancer-related or cancer treatment–related anemia occurs frequently in patients with lung cancer
- In a comprehensive review, Groopman JE et al reported incidences of anemia (Hb≤12 g/dL) and severe anemia (Hb<8 g/dL) as high as 100% and 55%, respectively, in patients with lung cancer receiving chemotherapy
- One major factor contributing to anemia in patients with lung cancer is the use of platinum-based chemotherapy as first-line chemotherapy
- Anemia is an independent prognostic factor for survival in patients with lung cancer*

J Natl Cancer Inst 1999;91:1616–1634
**Cancer 2001;91:2214–2221*

Anemia profiles in patients with lung cancer
THE EUROPEAN CANCER ANEMIA SURVEY (ECAS)



- Newly diagnosed, no treatment
- Newly diagnosed, with treatment
- Persistent or recurrent disease
- Remission

- 37.6% (753/2002) of lung cancer patients in the evaluable population were anemic
- Frequency of anemia in lung cancer patients increased during ECAS
- Hb nadirs were <9.0 g/dL in 21% of pts & ≤ 9.9 g/dL in 46% of pts
- Overall incidence of anemia was 70.9%
  - 79.6% for pts who received CT
  - 30.8% for pts who received concomitant CT/RT
  - 14.5% for pts who received RT

Lung Cancer. 2005 Dec;50(3):401-12. Epub 2005 Sep 26

Anemia profiles in patients with lung cancer

- Incidence of anemia was
  - 81.1% for pts who received platinum –based chemotherapy
  - 74.1% for pts who received non-platinum chemotherapy
- By Cycle 3, the proportion of pts receiving platinum chemotherapy who became anemic (64.9%) was nearly triple the proportion anemic at Cycle 1 (23.5%)
  - greater than the proportion of anemic patients receiving nonplatinum chemotherapy at that evaluation (51.6%; *P = 0.05; difference =−0.133, 95% CI* −0.2679, 0.0019)
- Mean time to anemia development for the platinum-treated patients were
  - 7.7 weeks to Hb 12 g/dL (*n = 174),*
  - *9.6 weeks to Hb 11 g/dL (n = 117),*and
  - 11.7 weeks to Hb 10 g/dL (*n = 54);*

Lung Cancer. 2005 Dec;50(3):401-12. Epub 2005 Sep 26

Anemia is important cause of intercycle delay

TABLE 1. Reasons for Intercycle Delays during Chemotherapy of Patients with NSCLC

Reason	Number[a] (Percentage of Total Cycles Delayed)
Unrelated to either disease or chemotherapy	
Nonavailability of reports of blood tests	24 (25.5%)
Hospital holiday on the scheduled day of chemotherapy	9 (9.6%)
Inability of the patient to come to the hospital on the scheduled day of chemotherapy because of personal reasons	6 (6.4%)
Administration of the previous cycle as inpatient	5 (5.3%)
Inability to get tumor response assessment done in intercycle time period	4 (4.3%)
Financial constraints	3 (3.2%)
Confusion about the scheduled day of chemotherapy	3 (3.2%)
Miscellaneous causes	4 (4.3%)
Related to disease or chemotherapy	
Grade 3/4 anemia	19 (20.2%)
Persistent vomiting/diarrhea related to the previous cycle of chemotherapy	7 (7.5%)
Poor performance status on the scheduled day of chemotherapy	4 (4.3%)
Active infection on the scheduled day of chemotherapy	3 (3.2%)
Chest tube insertion for management of symptomatic malignant pleural effusion	2 (2.1%)
Neutropenia	1 (1.1%)

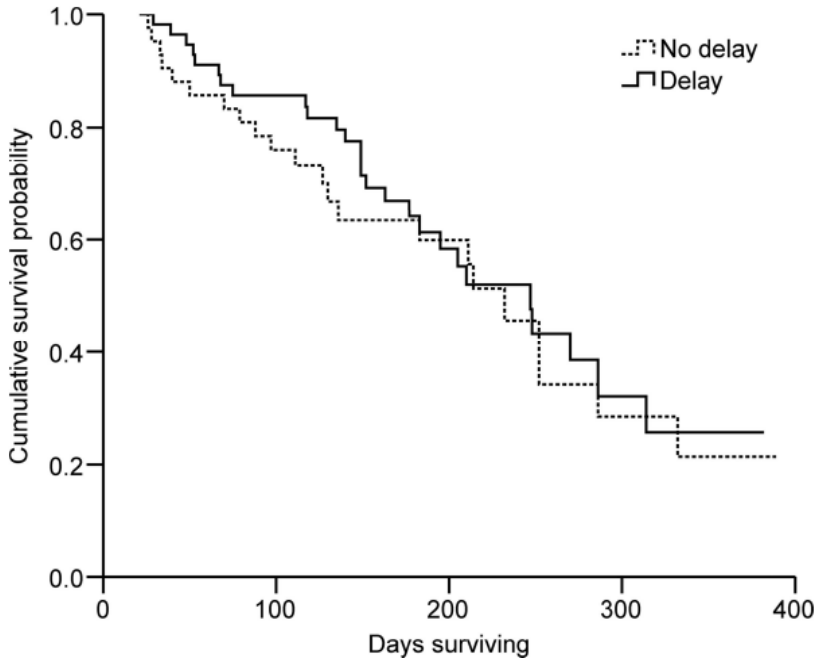


FIGURE 1. Probability of survival for patients experiencing intercycle delays (ICD) versus those not experiencing ICD (Kaplan-Meier analysis). The median survival in ICD+ and ICD− groups was similar (247 and 232 days, respectively, $p = 0.604$).

J Thorac Oncol. 2010;5: 236–239

Predicting anemia in lung cancer patients

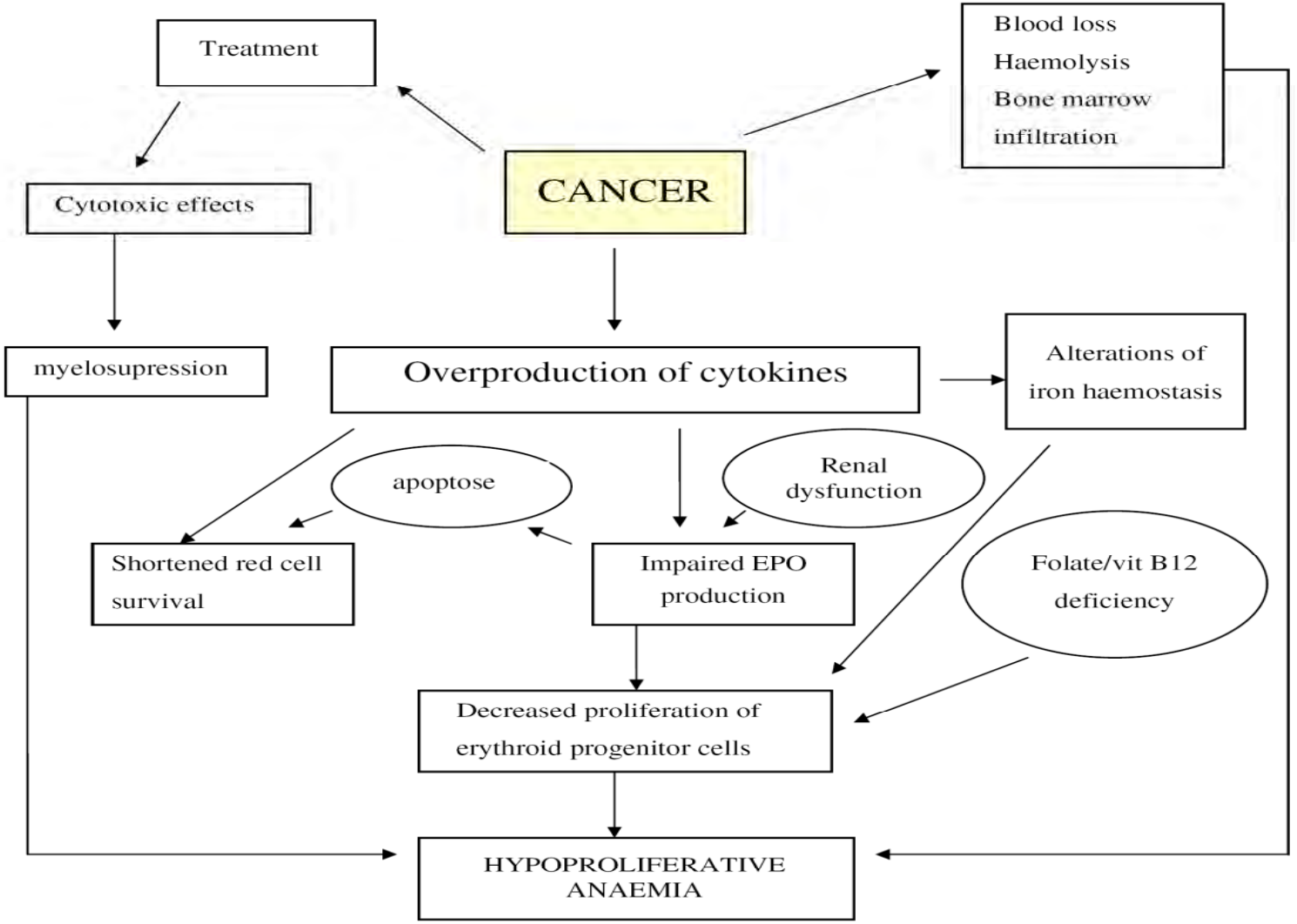
Table 3 Odds ratios and adjusted odds ratios for significant risk factors for anemia in lung cancer patients

	Odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Initial Hb[a]	0.7 (0.64–0.82)	<0.0001	0.7 (0.64–0.84)	<0.0001
Female sex	1.9 (1.25–2.77)	0.0024	1.7 (1.12–2.53)	0.0129
Treat with platinum	1.8 (1.31–2.50)	0.0003	2.1 (1.49–3.00)	0.0002

[a] Continuous variable: OR and AOR is for each 1-g/dL Hb increase over 12 g/dL.

Lung Cancer. 2005 Dec;50(3):401-12. Epub 2005 Sep 26

Mechanism of anemia



Med Oncol (2008) 25:12–21

Anemia As an Independent Prognostic Factor for Survival in Patients with Cancer

A Systematic, Quantitative Review

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Maribel Salas, M.D., D.Sc.[2]
Alexandra Ward, Ph.D.[2]
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BACKGROUND. Anemia is common in cancer patients, although the prevalence is influenced both by the type of malignancy and the choice of treatment. Individual studies have compared the survival of patients with and without anemia and have shown reduced survival times in patients with various malignancies, including carcinoma of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma. The objective of this study was to systematically review, to summarize, and to obtain an overall estimate of the effect of anemia on survival in patients with malignant disease.

METHODS. A comprehensive literature review was carried out using the MEDLINE data base and reviewing the reference lists from published studies. Two hundred papers were identified. Of these, 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.

RESULTS. The relative risk of death increased by 19% (95% confidence interval, 10–29%) in anemic patients with lung carcinoma, by 75% (37–123%) in anemic patients with head and neck carcinoma, by 47% (21–78%) in anemic patients with prostate carcinoma, and by 67% (30–113%) in anemic patients with lymphoma. The overall estimate increase in risk was 65% (54–77%).

CONCLUSIONS. Anemia is associated with shorter survival times for patients with lung carcinoma, cervicouterine carcinoma, head and neck carcinoma, prostate carcinoma, lymphoma, and multiple myeloma. ***Cancer* 2001;91:2214–21.**

Combined modality trials of the Cancer and Leukemia Group B in stage III non-small-cell lung cancer: analysis of factors influencing survival and toxicity

M. A. Socinski*, C. Zhang, J. E. Herndon II, R. O. Dillman, G. Clamon, E. Vokes, W. Akerley, J. Crawford, M. C. Perry, S. L. Seagren & M. R. Green

Cancer and Leukemia Group B, Chicago, IL, USA

Table 4. Proportional hazards model for survival

Variable	HR	95% CI	*P* value
Hemoglobin ≥ 12 g/dl	0.67	0.55–0.81	< 0.0001
Age ≥ 70 years	1.07	0.88–1.31	0.5
Male gender	1.04	0.88–1.24	0.628
Performance status 1	1.24	1.06–1.45	0.009
Weight loss ≥ 5%	1.04	0.73–1.47	0.841
TRT only	1.58	1.22–2.05	0.001
Sequential CH→TRT versus sequential → concurrent CH/TRT	1.01	0.85–1.20	0.933
WBC ≥ 12 000/mm^3	1.22	0.99–1.50	0.062

HR, hazard ratio; CI, confidence interval; TRT, thoracic radiation therapy; sequential CH → TRT, induction chemotherapy followed by TRT alone; sequential → concurrent CH/TRT, induction chemotherapy followed by concurrent chemoradiation; WBC, white blood cell count.

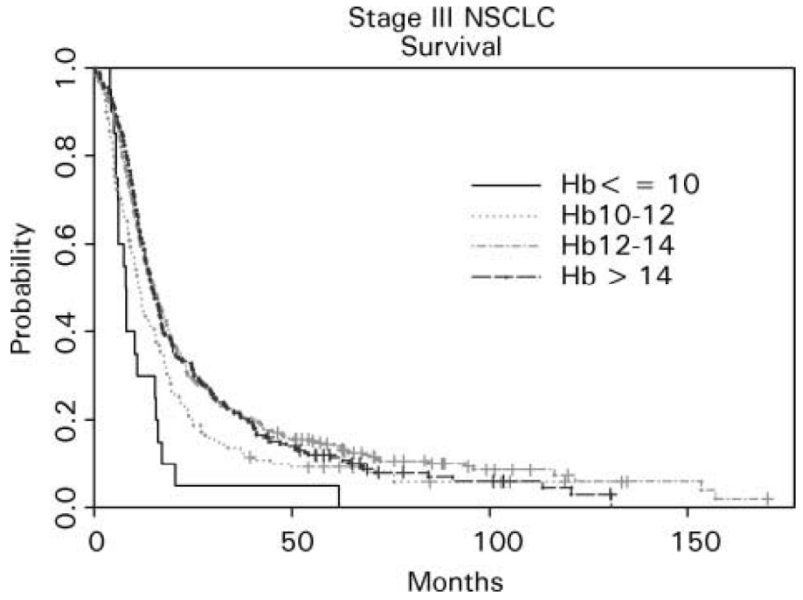
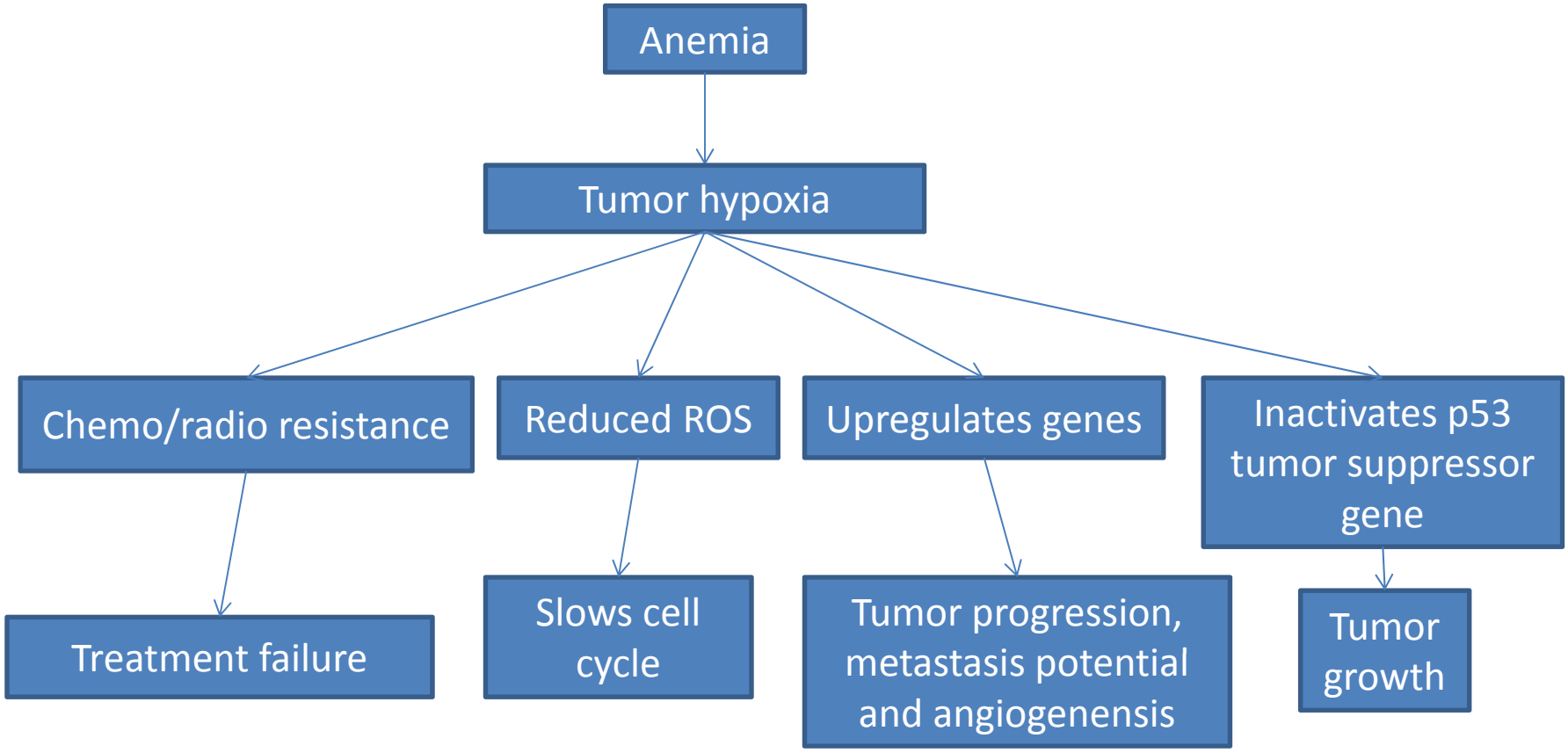


Figure 3. Overall survival curves for patients with unresectable stage III non-small-cell lung cancer based on baseline hemoglobin values.

Tumour hypoxia and response to treatment



Semin Oncol 2000;27(2 Suppl 4):4–8
Cancer J Sci Am 1998;4:218–23
Nature 1996;379:88–91

Anemia treatment is neglected!!!

- Data from the European Cancer Anaemia Survey (ECAS) published in 2003 suggest that
  - 60% of cancer patients who experienced anemia were given no treatment
  - Epoetin was given to 18% (median Hb level at initiation,9.9 g/dl)
  - 15% had a transfusion (median Hb at initiation,8.6 g/dl)
  - 7% were given only iron (Hb at initiation, 11.2g/dl)

Eur J Cancer 2004;40:2293–2306

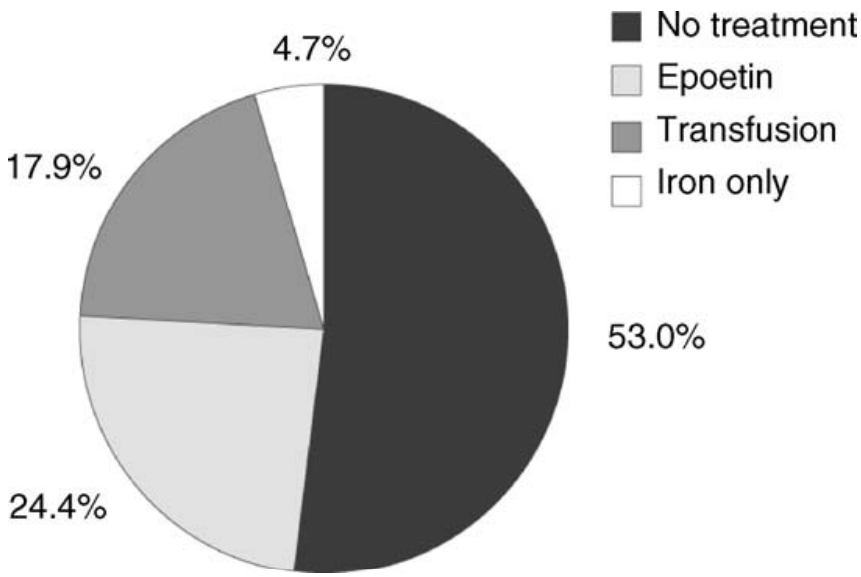
Influence of anemia on outcome of anticancer treatment

Study	Tumor	Treatment	Outcome	Hb level (g/dL)	Result (%)
Brizel (1999) [6]	Head and neck	Radiotherapy	3-yr OS	<13	35
				≥13	83[a]
Zenda et al. (2008) [7]	Esophagus	Chemoradiation	CR	<13	24
				≥13	60[a]
Grogan et al. (1999) [8]	Cervix	Radiotherapy	5-yr OS	<12	45
				≥12	74[a]
Dunst et al (2003) [9]	Cervix	Radiotherapy	3-yr LRFS	<13	72
				≥13	94[a]

[a] $p < .05$.
Abbreviations: CR, complete response; Hb, hemoglobin; LRFS, local relapse-free survival; OS, overall survival.

The Oncologist 2011;16(suppl 3):12–18

Anemia treatment during ECAS in lung cancer



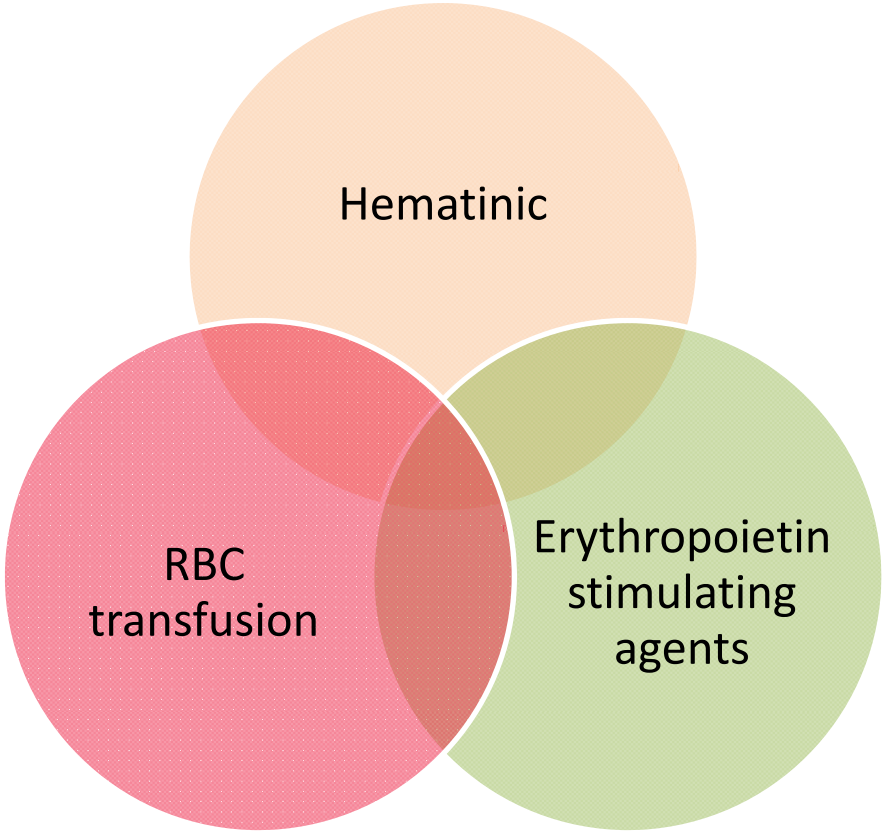
Percentages of patients treated for anemia (analysis population). ‘‘Epoetin’’ refers to the use of recombinant human erythropoietin alone or in combination with transfusion and/or iron; ‘‘transfusion’’ refers to the use of transfusion alone or in combination with iron; ‘‘iron’’ refers to the use of iron alone.

Lung Cancer. 2005 Dec;50(3):401-12. Epub 2005 Sep 26

- Data from ECAS indicate a high prevalence of anemia but less than optimal management of anemia in patients with lung cancer

- findings underscore the need for better anemia management in this high-risk population

Anemia treatment



Guidelines for RBC transfusions

Organization	Year	Indication for RBC transfusion
United Kingdom Blood Services	2007	Hb ≤9.0 g/dL
EORTC	2007	Hb <9.0 g/dL if clinically indicated
ASH/ASCO	2010	Hb <12.0 g/dL if clinically indicated
NCCN	2010	Asymptomatic: Hb 7–9 g/dL Symptomatic: Hb 8–10 g/dL Symptomatic coronary: Hb ≥10 g/dL

Abbreviations: ASH/ASCO, American Society of Hematology/American Society of Clinical Oncology; EORTC, European Organization for Research and Treatment of Cancer; Hb, hemoglobin; NCCN, National Comprehensive Cancer Network.

The Oncologist 2011;16(suppl 3):12–18

Complications of Transfusions

Procedural Problems

Iron Overload

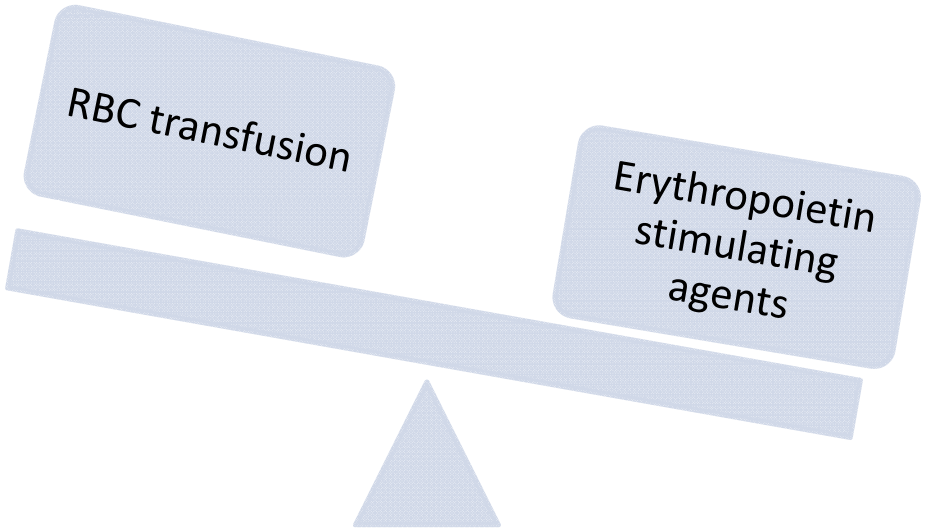
Viral and Bacterial Infectio

Immune Injury

Reaction	Incidence
Hemolytic transfusion reaction	1/10,000–1/50,000
Febrile nonhemolytic transfusion reaction	33/1,000
Anaphylactic transfusion reaction	1/20,000–1/47,000
Transfusion-related acute lung injury	1/2,500,000
Post-transfusion purpura	1/50,000–1/100,000
Transfusion-associated graft versus host disease	1/1,000–1/100[a]
Transfusion-related immunomodulation	
Alloimmunization after chronic transfusions	2/100–8/100

[a]In immunocompromised host.

The Oncologist 2011;16(suppl 3):12–18


RBC transfusion
Erythropoietin stimulating agents

Erythropoietin

- Acidic glycoprotein hormone
- Essential for proliferation and differentiation of erythroid precursors into mature cells
- Primary regulator of human erythropoiesis
- Kidney = 90% of hormone and 10% in liver and elsewhere
- First haemopoietic growth factor to be cloned in 1985

Erythropoietin stimulating agents

ESA	Marketed as	T1/2	Cost
Epoetin alfa	Procrit®,Johnson & Johnson, Brunswick, NJ Epogen®, Amgen Inc, Thousand Oaks, CA	24 h	INR 8000-15000/wk
Epoetin beta	NeoRecormon®, Roche, Basel, Switzerland	20.5 h	INR 10000/wk
Darbepoetin alfa	Aranesp®, Amgen Inc; Cresp® Dr Reddy's	~ 49 h	INR 24000 for 500 mcg
CERA	(Continuous Erythropoietin Receptor Activator, Roche)		

Effectiveness of ESA in Lung cancer

- Need of RBC transfusions
- Hemoglobin response
- Quality of life
- Tumor growth & Survival
- Potential adverse outcomes
- Difference in efficacy among ESAs

Comprehensive review

Clinical Benefits of Epoetin Alfa Therapy in Patients with Lung Cancer

Jeffrey Crawford,[1] George D. Demetri,[2] Janice L. Gabrilove,[3] Michael V. Blasi,[4] Brenda J. Sarokhan,[4] John Glaspy[5]

Abstract

A retrospective subset analysis of anemic lung cancer patients who participated in three large, multicenter, community-based studies of 3-times-weekly (TIW) or once-weekly (QW) recombinant human erythropoietin (r-HuEPO, epoetin alfa) as an adjunct to chemotherapy was conducted. Patients were treated with epoetin alfa 150 U/kg in the first TIW study and with 10,000 U subcutaneously in the other study, with doubling of the dose if hemoglobin (Hb) response was inadequate. Patients in the QW study received epoetin alfa 40,000 U subcutaneously, which could be increased to 60,000 U. The maximum treatment duration for all three studies was 16 weeks. A total of 1748 lung cancer patients were evaluable for hematopoietic response; 1298 were evaluable for analyses of energy and 1300 were evaluable for analyses of activity and overall quality of life (QOL), as measured by the linear analogue scale assessment (LASA). Within 2 months of therapy, TIW and QW epoetin alfa therapy resulted in significant increases in Hb levels, decreases in transfusion requirements, and improvements in self-reported LASA scores. Increased Hb levels and reduced transfusion rates were demonstrated in the individual studies and in the analysis of data pooled from all three studies. Improvements in QOL parameters were significantly correlated with increased Hb levels. Epoetin alfa was well tolerated in all studies. The clinical benefits and safety profiles of the TIW and the QW schedules appear to be similar. In addition, the QW schedule provides greater convenience to patients and physicians alike. Given the high incidence of anemia and transfusion utilization in patients presenting with lung cancer, epoetin alfa is an effective strategy for correcting anemia in these patients, thereby improving their energy levels, activity levels, and overall QOL.

Clinical Lung Cancer, Vol. 3, No. 3, 180-190, 2002

Key words: Anemia, Erythropoietin, Hemoglobin, Transfusions, Quality of life, Neoplasm

Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy

Johan Vansteenkiste, Robert Pirker, Bartomeu Massuti, Fernando Barata, Albert Font, Michael Fiegl, Salvatore Siena, Jenni Gateley, Dianne Tomita, Alan B. Colowick, Jaromir Musil

For the Aranesp™ 980297 Study Group

- N= 314
- Darbepoetin alfa (2.25 mcg/kg SC once weekly)
- Baseline Hb ≤ 11g/dl

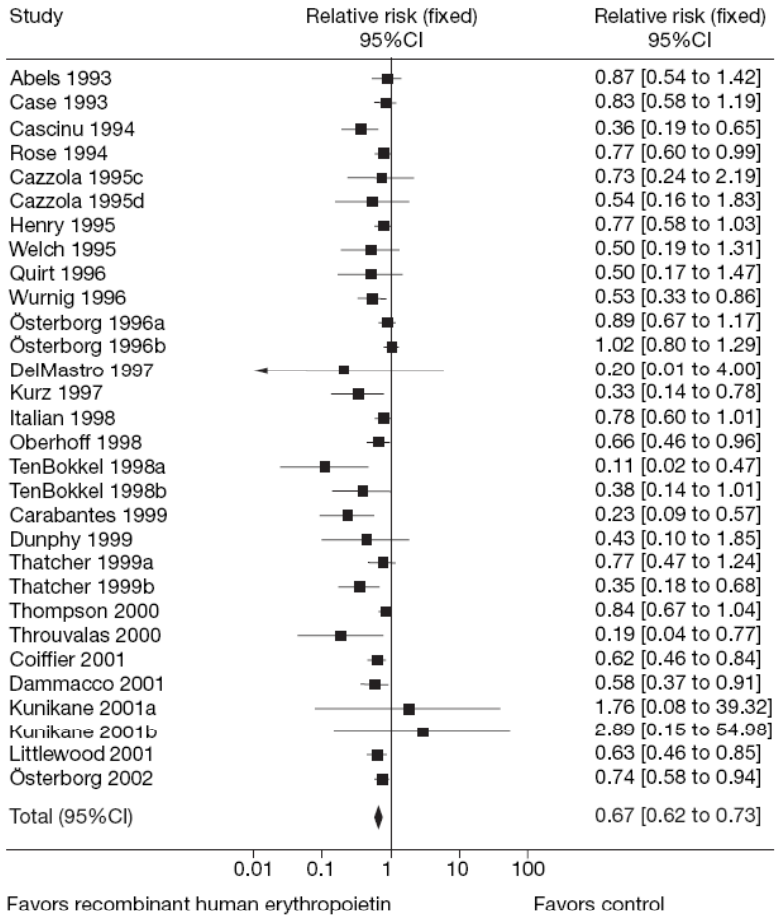
- No significant difference
  - median progression-free survival(22 versus 20 weeks),
  - overall mortality (59% versus 69%), or
  - median duration of survival (46 weeks versus 34 weeks) t 1-year follow up

- N= 314
- Darbepoetin alfa (2.25 mcg/kg SC once weekly)
- Baseline Hb ≤ 11g/dl

- Hematopoietic response (Hb increase 2 g/dL or Hb 12 g/dL in the absence of transfusion within the previous 28 days) was achieved in 66% vs 24% of placebo patients (*p .001)*

J Natl Cancer Inst 2002;94:1211–20

Meta-analysis of the relative risk to receive red blood cell transfusions for cancer patients receiving erythropoietin or standard care



- 25 randomized controlled trials
- 3,069 patients
- RR 0.67,95% CI 0.62–0.73

Applied to an estimated risk of 50% to receive RBC transfusions, the number needed to treat is 6.06 (95% CI 5.26–7.41)

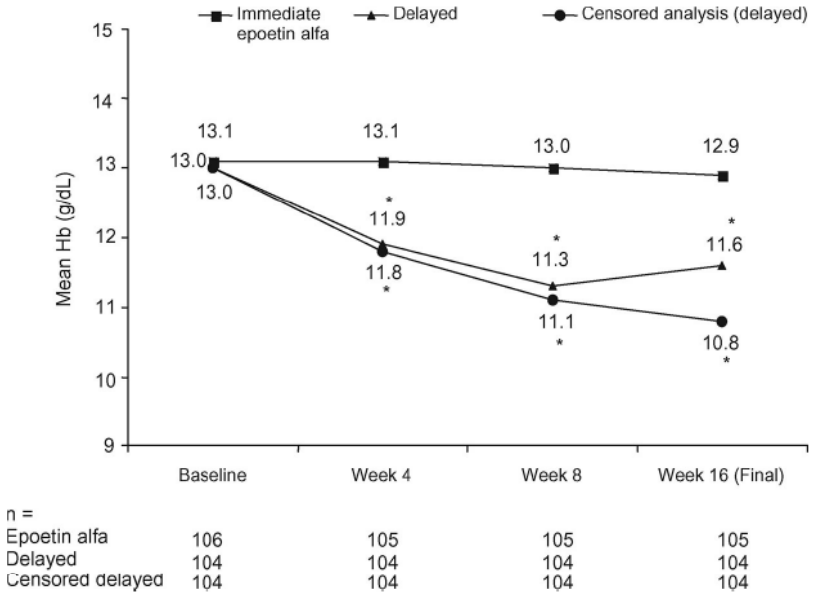
RR for hematologic response in the EPO group was 3.60 (95% CI 3.07–4.23)

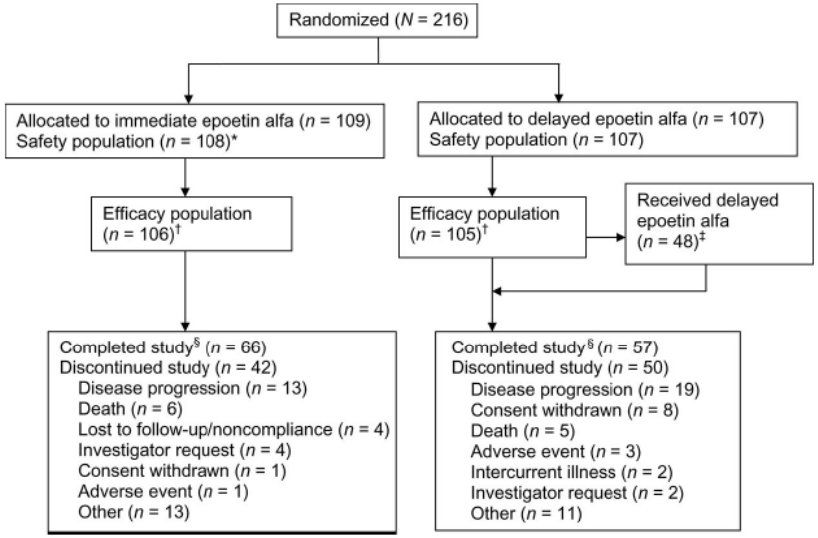
www.nature.com/clinicalpractice/onc
MARCH 2006 VOL 3 NO 3

The Cochrane Database of Systematic Reviews, Issue 3, Art. No CD003407

A Randomized Trial Comparing Immediate versus Delayed Treatment of Anemia with Once-Weekly Epoetin Alfa in Patients with Non-small Cell Lung Cancer Scheduled to Receive First-Line Chemotherapy

Jeffrey Crawford, MD, Francisco Robert, MD,† Michael C. Perry, MD,‡ Chandra Belani, MD,§ and Denise Williams, MD,|| for the Anemia Prevention in NSCLC Group*





J Thorac Oncol. 2007;2: 210–220

Early intervention with epoetin beta prevents severe anaemia in lung cancer patients receiving platinum-based chemotherapy: a subgroup analysis of the NeoPrevent study.

de Castro J, Belda-Iniesta C, Isla D, Dómine M, Sánchez A, Batiste E, Barón MG.

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Abstract

The NeoPrevent study showed that early intervention with epoetin beta could prevent severe anaemia in patients with solid tumours receiving platinum-based chemotherapy. An early intervention strategy may be particularly warranted in patients with lung cancer, as anaemia is very common in these patients and can be severe. The purpose of this study was to examine the efficacy and safety of epoetin beta in the subpopulation of patients with lung cancer included in the NeoPrevent study. Patients were enrolled if baseline haemoglobin (Hb) levels were <or=13 g/dl (men) or <or=12 g/dl (women), or fell to these levels during platinum-based chemotherapy. Patients received epoetin beta 150 IU/kg three times weekly, until 4 weeks after last chemotherapy cycle. The anaemia prevention response was measured as the proportion of patients with an Hb response (Hb increase of >1g/dl) plus the proportion whose Hb was maintained at +/-1g/dl of baseline. Quality of life (QoL) was measured using the linear analogue scale assessment. The NeoPrevent study included 255 patients in total, and the results for the 102 patients with lung cancer (non-small-cell lung cancer 64%; small-cell lung cancer 36%) are presented here. The overall anaemia prevention response was 90%, with Hb response in 60% of patients and maintenance of baseline Hb level in 30%. Only 9% of patients required transfusions. QoL improved significantly in patients with Hb response (p<0.01) and was maintained in non-responders (p>or=0.578). Epoetin beta was effective in preventing severe anaemia in lung cancer patients receiving platinum-based chemotherapy.

Lung Cancer. 2008 Feb;59(2):211-8.

Comparative efficacy and safety of epoetin and darbepoetin

Agency for Healthcare Research and Quality. May 2006

Table A. Summary of Rates of Hematologic Response, Transfusion, and Thromboembolic Events

Parameter	Darbepoetin vs. epoetin	Epoetin vs. control	Darbepoetin vs. control
Hb response rates: Number of studies reporting	6	15	3
Patients analyzed	2,205	3,293	659
Pooled relative risk of Hb increase ≥2 mg/dL (95% CI)	Meta-analysis not done[1]	3.42 (3.03, 3.86)[2]	3.36 (2.48, 4.56)
Pooled event rates (range across studies)	Meta-analysis not done[1]	Epo: 58% (21%–73%) Control: 17% (3%–32%)	Darb: 54% (25%–84%) Control: 17% (9%–18%)
Transfusion rates: Number of studies reporting	6	34	4
Patients analyzed	2,158	5,210	950
Pooled relative risk (95% CI)	1.10 (0.93, 1.29)[2]	0.63 (0.59, 0.67)[2]	0.61 (0.52, 0.72)
Pooled event rates (range across studies)	Darb: 22% (3%–28%) Epo: 20% (12%–43%)	Epo: 30% (0–91%) Control: 47% (0–100%)	Darb: 29% (13%–34%) Control: 51% (25%–67%)
Thromboembolic events: Number of studies reporting	3	30	1
Patients analyzed	1,879	6,092	314
Pooled relative risk (95% CI)	0.86 (0.61, 1.21)	1.69 (1.36, 2.10)	1.44 (0.47, 4.43)[3]
Pooled event rates (range across studies)	Darb: 6% (3%–9%) Epo: 7% (3%–11%)	Epo: 7% (0–30%) Control: 4% (0–23%)	Darb: 5% Control: 3%

[1] Trials defined response differently and initiated and adjusted doses differently; only one randomized controlled trial (n=352) reported significant difference favoring epoetin, but results may be biased since dose was adjusted differently in each arm; five trials (N=1,853) reported no significant differences between arms.

[2] Tests of heterogeneity (I^2) indicated excessive variability among individual study results. Results of this fixed-effects meta-analysis were compared with random-effects meta-analysis; results were not meaningfully different.

[3] Since there was only one trial, this result is a single-study (not pooled) relative risk.

Abbreviations: CI: confidence interval; Hb: hemoglobin.

No clinically significant difference between epoetin and darbepoetin in hemoglobin response, transfusion reduction, and thromboembolic events

Alternative dosing strategies

- 12 trials examined different dosing regimens for epoetin and seven trials examined different dosing regimens for darbepoetin.
- For each of the following pairs of dosing strategies, one large trial reported no statistically significant difference between strategies:
  - fixed-dose compared to dose based on weight, one trial each for epoetin and darbepoetin;
  - fixed-dose epoetin administered weekly vs. thrice weekly;
  - fixed dose epoetin administered weekly vs. every 3 weeks; and
  - darbepoetin using an initial loading dose versus constant weight-based dosing regimens.
- The remaining 14 trials were too small to interpret
- Dose conversion ratio [IU epoetin alfa:mcg darbepoetin alfa]) was 199:1

Risks of erythropoiesis-stimulating agent treatments: concerns about tumour progression

- Some in-vitro studies showed that tumour cells treated with ESA might display an enhanced proliferation rate and apoptosis resistance
- Henke et al. studied clinical impact of presence of EPORs on cell surface in head and neck cancer patients.
  - In the EPOR+ group the locoregional progression-free survival was substantially lower in patients treated with ESA

Lancet 2003; 362:1255–1260

- BEST study, carried out on 939 breast cancer patients receiving chemotherapy was terminated prematurely due to a greater rate of mortality (8.7 versus 3.4%) and a higher rate of fatal thrombotic events in the EPO arm (1.1 versus 0.2%)

J Clin Oncol 2005; 23:5960–5972

- PREPARE study, a double-blind placebo controlled phase III trial that randomized 733 breast cancer patients, showed no differences in tumour response to neoadjuvant chemotherapy between the two groups. A higher mortality rate was, however, found in patients receiving ESA treatment

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

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A B S T R A C T

Purpose
Previous trials have suggested a quality-of-life (QOL) improvement for anemic cancer patients treated with erythropoietin, but few used QOL as the primary outcome. We designed a trial to investigate the effects of epoetin alfa therapy on the QOL of anemic patients with advanced non–small-cell carcinoma of the lung (NSCLC).

Patients and Methods
A multicenter, randomized, double-blind, placebo-controlled trial was conducted. The proposed sample size was 300 patients. Eligible patients were required to have NSCLC unsuitable for curative therapy and baseline hemoglobin (Hgb) levels less than 121 g/L. Patients were assigned to 12 weekly injections of subcutaneous epoetin alpha or placebo, targeting Hgb levels between 120 and 140 g/L. The primary outcome was the difference in the change in Functional Assessment of Cancer Therapy–Anemia scores between baseline and 12 weeks.

Results
Reports of thrombotic events in other epoetin trials prompted an unplanned safety analysis after 70 patients had been randomly assigned (33 to the active arm and 37 to the placebo arm). This revealed a significant difference in the median survival in favor of the patients on the placebo arm of the trial (63 *v* 129 days; hazard ratio, 1.84; $P = .04$). The Steering Committee closed the trial. Patient numbers compromised the interpretation of the QOL analysis, but a positive Hgb response was noted with epoetin alfa treatment.

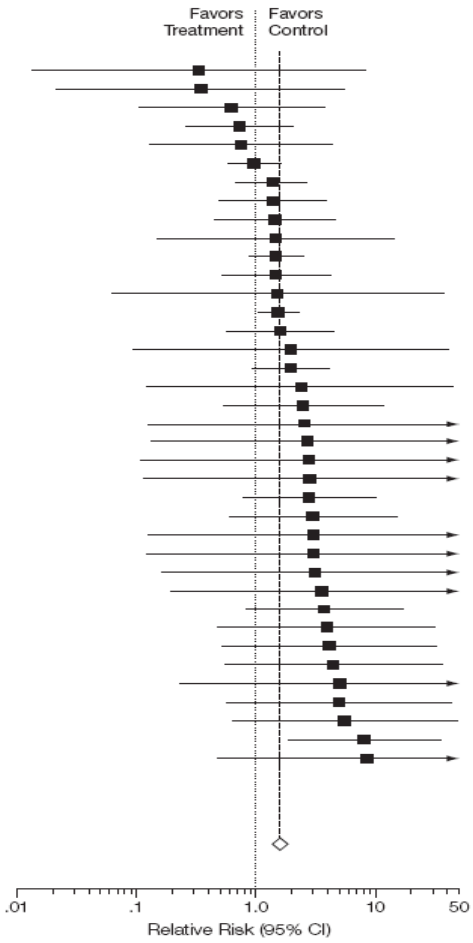
Conclusion
An unplanned safety analysis suggested decreased overall survival in patients with advanced NSCLC treated with epoetin alfa. Although infrequent, other similar reports highlight the need for ongoing trials evaluating erythropoietin receptor agonists to ensure that overall survival is monitored closely.

J Clin Oncol 25:1027-1032. © 2007 by American Society of Clinical Oncology

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

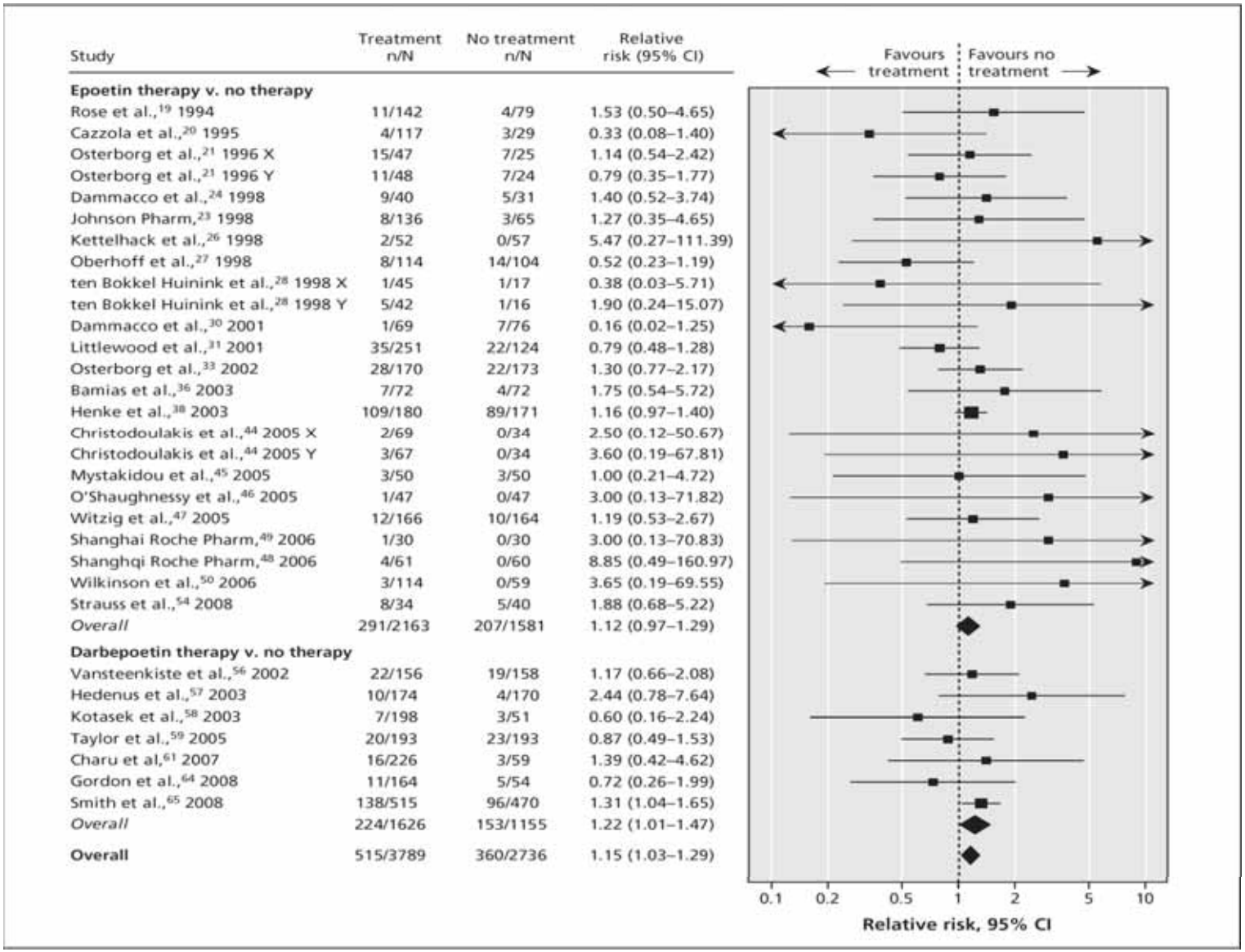
Figure 3. Meta-analysis of VTE Rates in Phase 3 Trials of ESAs vs Placebo or Control

Source	No. of VTE Events/Total No. (%) Treatment	Control	Weight, %	Relative Risk (95% CI)
Bamias et al,[29] 2003	0/72 (0)	1/72 (1)	0.31	0.33 (0.01-8.05)
Smith et al,[52] 2003	1/64 (2)	1/22 (5)	0.42	0.34 (0.02-5.27)
Case et al,[30] 1993	2/81 (2)	3/76 (4)	1.02	0.63 (0.11-3.64)
Henry and Abels,[36] 1994	6/67 (9)	8/65 (12)	3.14	0.73 (0.27-1.98)
Wright et al,[58] 2007 (EPO-CAN-20)	2/33 (6)	3/37 (20)	1.06	0.75 (0.13-4.20)
Grote et al,[43] 2005 (N93-004)	24/109 (22)	26/115 (23)	13.20	0.97 (0.60-1.59)
EPO-CAN-17,[12] 2007	19/175 (11)	14/175 (8)	7.29	1.36 (0.70-2.62)
Littlewood et al,[41] 2001	14/251 (6)	5/124 (4)	3.17	1.38 (0.51-3.75)
Vansteenkiste et al,[2] 2002	7/155 (2)	5/159 (3)	2.49	1.44 (0.47-4.43)
INT-1,[11] 2004	3/164 (2)	1/80 (1)	0.62	1.46 (0.15-13.85)
Leyland-Jones et al,[40] 2005 (INT-76)	36/448 (8)	25/456 (5)	12.97	1.47 (0.89-2.40)
Witzig et al,[57] 2005	9/168 (5)	6/165 (4)	3.09	1.47 (0.54-4.05)
Osterborg et al,[46] 1996	1/48 (2)	0/24 (0)	0.32	1.53 (0.06-36.23)
Amgen DA 145,[13] 2007	66/298 (22)	43/298 (14)	25.92	1.53 (1.08-2.18)
Henke et al,[5] 2003	10/180 (6)	6/171 (4)	3.22	1.58 (0.59-4.26)
ten Bokkel Huinink et al,[53] 1998	2/45 (4)	0/17 (0)	0.35	1.96 (0.10-38.79)
Debus et al,[16] 2007 (EPO-GER-22)	20/108 (19)	10/107 (9)	6.25	1.98 (0.97-4.03)
Charu et al,[15] 2007			0.37	2.36 (0.13-43.20)
Rose et al,[50] 1994	9/142 (6)	2/79 (3)	1.39	2.50 (0.55-11.30)
Thatcher et al,[54] 1999	2/44 (5)	0/22 (0)	0.35	2.56 (0.13-51.05)
Osterborg et al,[46] 1996	2/47 (4)	0/25 (0)	0.35	2.71 (0.14-54.32)
Abels,[28] 1993	1/65 (2)	0/59 (0)	0.31	2.73 (0.11-65.68)
Throuvalas et al,[55] 2000	1/28 (4)	0/26 (0)	0.32	2.79 (0.12-65.66)
GOG-191,[11] 2007	9/58 (16)	3/55 (5)	2.01	2.84 (0.81-9.96)
Razzouk et al,[49] 2004	6/112 (5)	2/110 (2)	1.27	2.95 (0.61-14.28)
Welch et al,[61] 1995	1/15 (7)	0/15 (0)	0.32	3.00 (0.13-68.26)
Osterborg et al,[47] 2005	1/170 (1)	0/173 (0)	0.31	3.05 (0.13-74.41)
Gordon et al,[17] 2006	4/162 (16)	0/56 (5)	0.37	3.15 (0.17-57.55)
ten Bokkel Huinink et al,[53] 1998	4/42 (10)	0/16 (0)	0.38	3.56 (0.20-62.58)
Vadhan-Raj et al,[56] 2004	7/29 (24)	2/31 (6)	1.43	3.74 (0.85-16.56)
INT-3,[11] 2004	8/135 (6)	1/65 (2)	0.75	3.85 (0.49-30.15)
Wilkinson et al,[20] 2006	12/173 (7)	1/59 (2)	0.77	4.09 (0.54-30.80)
Savonije et al,[51] 2004	9/211 (4)	1/104 (1)	0.75	4.44 (0.57-34.55)
Machtay et al,[42] 2007 (RTOG 99-03)	2/71 (3)	0/70 (0)	0.35	4.93 (0.24-100.89)
EPO-GBR-7,[12] 2007	5/151 (3)	1/149 (1)	0.69	4.93 (0.58-41.73)
Dammacco et al,[33] 2001	5/69 (7)	1/76 (1)	0.70	5.51 (0.66-45.98)
EPO-CAN-15,[11] 2004	16/53 (30)	2/53 (4)	1.57	8.00 (1.93-33.09)
Rosenzweig et al,[60] 2004	4/14 (29)	0/13 (0)	0.39	8.40 (0.50-142.27)
Cascinu et al,[59] 1994	0/50 (0)	0/50 (0)	0	
P-174,[11] 2004	0/33 (0)	0/12 (0)	0	
Thatcher et al,[54] 1999	0/42 (0)	0/22 (0)	0	
Overall $I^2=0\%$; $P=.88$			100.00	1.57 (1.31-1.87)



VTE indicates venous thromboembolism; ESA, erythropoiesis-stimulating agent; CI, confidence interval. Weights are from random-effects analysis. Some trials are represented more than once due to having more than 1 group within the trial. Each ESA-containing group in these trials evaluated different doses of ESAs in comparison with controls. The point estimates and CIs for the bottom 3 trials could not be calculated because no events were reported in these studies.

Effect of treatment with ESAs vs no treatment on all-cause mortality



Study	Treatment n/N	No treatment n/N	Relative risk (95% CI)
Epoetin therapy v. no therapy			
Rose et al.,[19] 1994	11/142	4/79	1.53 (0.50–4.65)
Cazzola et al.,[20] 1995	4/117	3/29	0.33 (0.08–1.40)
Osterborg et al.,[21] 1996 X	15/47	7/25	1.14 (0.54–2.42)
Osterborg et al.,[21] 1996 Y	11/48	7/24	0.79 (0.35–1.77)
Dammacco et al.,[24] 1998	9/40	5/31	1.40 (0.52–3.74)
Johnson Pharm,[23] 1998	8/136	3/65	1.27 (0.35–4.65)
Kettelhack et al.,[26] 1998	2/52	0/57	5.47 (0.27–111.39)
Oberhoff et al.,[27] 1998	8/114	14/104	0.52 (0.23–1.19)
ten Bokkel Huinink et al.,[28] 1998 X	1/45	1/17	0.38 (0.03–5.71)
ten Bokkel Huinink et al.,[28] 1998 Y	5/42	1/16	1.90 (0.24–15.07)
Dammacco et al.,[30] 2001	1/69	7/76	0.16 (0.02–1.25)
Littlewood et al.,[31] 2001	35/251	22/124	0.79 (0.48–1.28)
Osterborg et al.,[33] 2002	28/170	22/173	1.30 (0.77–2.17)
Bamias et al.,[36] 2003	7/72	4/72	1.75 (0.54–5.72)
Henke et al.,[38] 2003	109/180	89/171	1.16 (0.97–1.40)
Christodoulakis et al.,[44] 2005 X	2/69	0/34	2.50 (0.12–50.67)
Christodoulakis et al.,[44] 2005 Y	3/67	0/34	3.60 (0.19–67.81)
Mystakidou et al.,[45] 2005	3/50	3/50	1.00 (0.21–4.72)
O'Shaughnessy et al.,[46] 2005	1/47	0/47	3.00 (0.13–71.82)
Witzig et al.,[47] 2005	12/166	10/164	1.19 (0.53–2.67)
Shanghai Roche Pharm,[49] 2006	1/30	0/30	3.00 (0.13–70.83)
Shanghqi Roche Pharm,[48] 2006	4/61	0/60	8.85 (0.49–160.97)
Wilkinson et al.,[50] 2006	3/114	0/59	3.65 (0.19–69.55)
Strauss et al.,[54] 2008	8/34	5/40	1.88 (0.68–5.22)
Overall	291/2163	207/1581	1.12 (0.97–1.29)
Darbepoetin therapy v. no therapy			
Vansteenkiste et al.,[56] 2002	22/156	19/158	1.17 (0.66–2.08)
Hedenus et al.,[57] 2003	10/174	4/170	2.44 (0.78–7.64)
Kotasek et al.,[58] 2003	7/198	3/51	0.60 (0.16–2.24)
Taylor et al.,[59] 2005	20/193	23/193	0.87 (0.49–1.53)
Charu et al,[61] 2007	16/226	3/59	1.39 (0.42–4.62)
Gordon et al.,[64] 2008	11/164	5/54	0.72 (0.26–1.99)
Smith et al.,[65] 2008	138/515	96/470	1.31 (1.04–1.65)
Overall	224/1626	153/1155	1.22 (1.01–1.47)
Overall	515/3789	360/2736	1.15 (1.03–1.29)

CMAJ 2009;180(11):E62-E71

Indications for the use of ESAs

Anemic patients with non-myeloid malignancies

- In patients treated with chemotherapy and an Hb concentration of≤10 g/dl, treatment with ESAs might be considered to increase Hb to <12 g/dl or to prevent a further decline in Hb [I, A].
- In patients treated with chemotherapy and an Hb concentration of 10–12.0 g/dl, treatment with ESAs could be considered in the case of symptoms or to prevent a further decline in Hb [I, A].
  - However, this is an off-label indication.
- In patients not treated with chemotherapy, there is no indication for the use of ESAs since there might be an increased risk of death when ESAs are administered to a target Hb of 12 g/dl [I, A].
- In patients treated with curative intent, ESAs should be used with caution [D]

Ann Oncol 2008;19(Suppl 2): ii113–ii115

Indications for the use of ESAs

Anemic patients with non-myeloid malignancies

- If the Hb increase is at least 1 g/dl above baseline after 4 weeks of treatment, the dose may remain the same or may be decreased by 25–50%.
- If the Hb increase is <1 g/dl above baseline, the dose of selected ESA should be increased. If after an additional 4 weeks of therapy, the Hb has increased≥1 g/dl the dose may remain the same or may be decreased by 25–50%.
- In the case of response, treatment with ESAs should be discontinued 4 weeks after the end of chemotherapy.
- If the Hb increase is <1 g/dl above baseline after 8–9 weeks of therapy, response to ESAs therapy is unlikely and treatment should be discontinued.
- If the Hb rises by >2 g/dl per 4 weeks or if the Hb exceeds 12 g/dl, the dose should be reduced by 25–50%.
- If the Hb exceeds 12 g/dl, therapy should be discontinued until Hb falls below 12 g/dl and then reinstituted at a dose 25% below the previous dose.

Ann Oncol 2008;19(Suppl 2): ii113–ii115

Treatment recommendations according to label [European Medicine Agency (EMEA)]

	Epoetin α	Epoetin β	Darbepoetin
Initial treatment	150 IU/kg s.c. TIW	30 000 IU s.c. QW	2.25 μg/kg s.c. QW
	450 IU/kg s.c. QW		500 μg (6.75 μg/kg) s.c. Q3W
Dose increase	300 IU/kg s.c. TIW	60.000 IU s.c. QW	Not recommended
Dose reduction	If result achieved: 25–50%	If result achieved: 25–50%	If result achieved: 25–50%
	If Hb >12 g/dl: 25–50%	If Hb >12 g/dl: 25–50%	If Hb >12 g/dl: 25–50%
	If Hb rise >2 g/dl/4 weeks: 25–50%	If Hb rise >2 g/dl/4 weeks: 25–50%	If Hb rise >2 g/dl/4 weeks: 25–50%
Dose witholding	If Hb >13 g/dl until 12 g/dl	If Hb >13 g/dl until 12 g/dl	If Hb >13 g/dl until 12 g/dl

s.c., subcutaneous; TIW, thrice weekly; QW, once weekly; Q3W, once every 3 weeks.

Ann Oncol 2008;19(Suppl 2): ii113–ii115

Summary

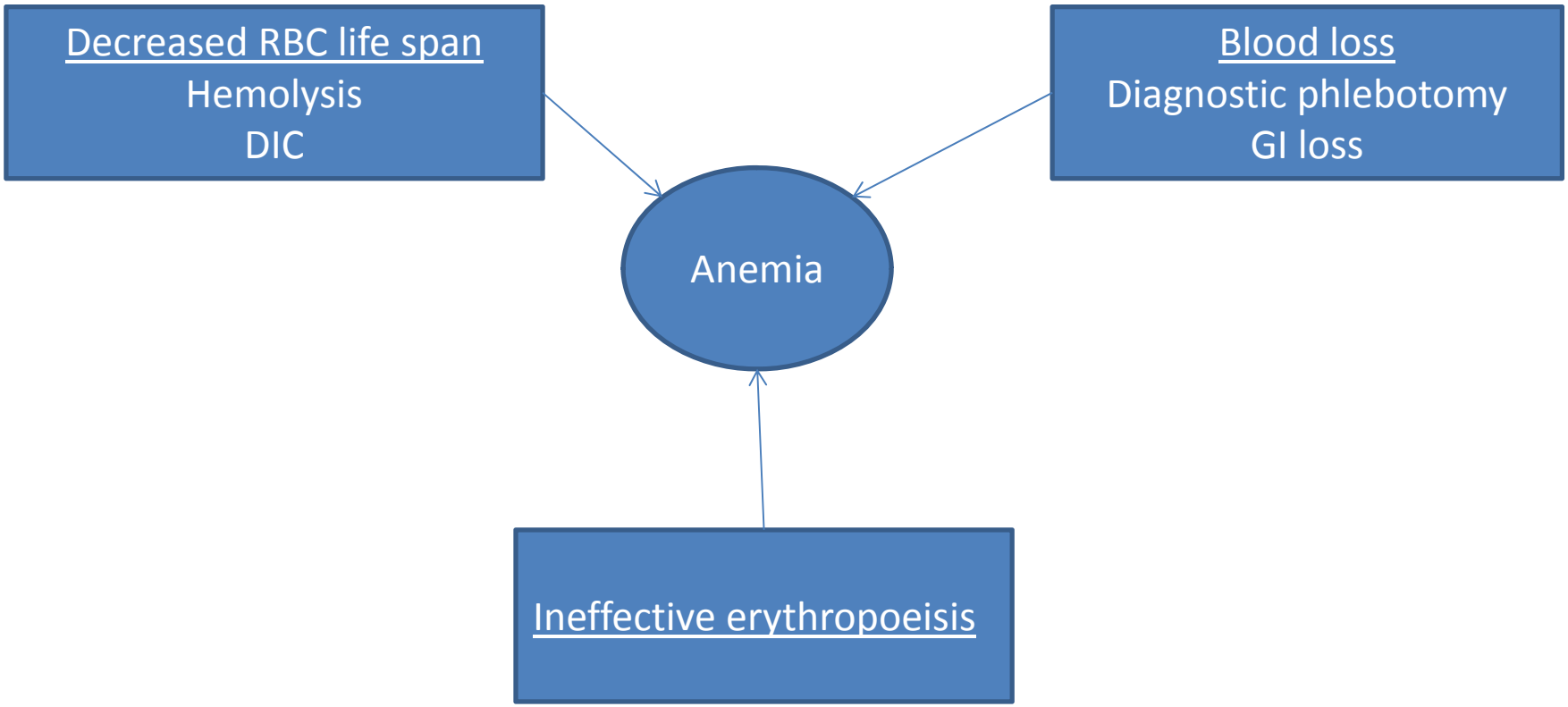
- Avoidance of transfusions
  - ESAs reduces significantly the RR of receiving RBCTs by 36% [relative risk (RR) 0.64, 95% CI 0.60–0.68]
- Treatment with ESAs in patients with chemotherapy-induced anemia increases Hb levels with an overall weighted mean difference of 1.63 g/dl [95% confidence interval (CI): 1.46–1.80 g/dl] compared with controls
- Positive impact on quality of life
- No overall survival benefit
- Risks of thromboembolic events
- Cost-effectiveness in our set-up needs to be proven
- Need indigenous guideline for mgmt of anemia in cancer

Anemia in critical illness

- Common and appears early during ICU course
- Almost 95% of pts are anemic by day 3 of ICU admission
- Anemia persists throughout ICU and hospital stay with or without RBC transfusion

Crit Care Med 1999, 27:2346-2350
J Crit Care 2001, 16:36-41
Crit Care Med 2004, 32:39-52

Mechanism of anemia in critical illness



Blood transfusions in ICU

- >50% of pts receive RBC transfusions during their ICU stay
- > 85% for those staying > 1 week
- ~ 14 % medical & 25 % surgical pts receive transfusions everyday in ICU
- On average, 9.5 RBC units were transfused during their ICU stay
- These transfusions are not restricted to the early ICU course; rather, patients are transfused at a rate of 2–3 units per week

Chest 1995; 108:767–771

Management of anemia in ICU

- Low Hb was synchronous with poor O2 delivery & tissue hypo perfusion
- Maintaining high Hb was thought to improve mortality
- Since 1942, rule of 10 / 30 was followed with no RCTs to back up the argument

- Randomized medical and surgical critically ill patients to either a liberal transfusion strategy (hemoglobin goal, 10.0 to 12.0 g/dL, with a transfusion trigger of 10.0 g/dL) or to a restrictive approach (hemoglobin goal, 7.0 to 9.0 g/dL, with a transfusion trigger of 7.0 g/dL).
- Trial demonstrated that a restrictive strategy was equivalent to a liberal transfusion strategy.
- In patients who were less acutely ill (APACHE II score 20) or 55 years of age, the restrictive strategy was superior and was associated with a decrease in mortality.

NEJM 1999; 340(6) February 11

Why liberal transfusion is counterproductive ?

- Exact reason is unclear
- Proposed mechanisms include
  - Storage lesion effect
  - TRIM (transfusion related immunomodulation)

Other important RCTs

- Blood transfusions:
  - CRIT Study [Crit Care Med 2004;32: 39-52]
  - Blood Observational Study [Critical Care 2011; 15: R116]
- ESAs:
  - JAMA 2002; 288: 2827-35
  - NEJM 2007; 357(10) September 06