Anemia in the Elderly

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“Anemia should not be accepted as an inevitable consequence of aging”

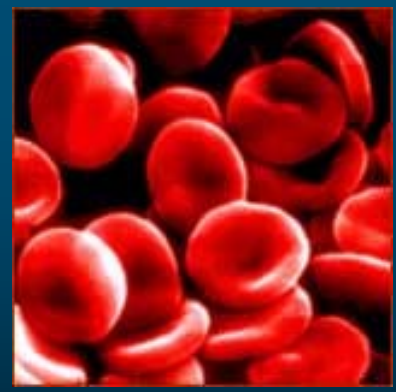
A cause is found in approximately 80 percent of elderly patients

Anemia: Geriatric Patients

- Common occurrence, although usually mild
- High prevalence in nursing homes - 31.4%
  - (a) anemias due to causes more common in the elderly;
  - (b) anemias without special predilection for the elderly;
  - (c) anemias of unknown cause (up to 17%)

Geriatric-Related Anemia

- Anemia of chronic disease
- Renal insufficiency
- Blood loss
- Bone marrow infiltration
- Nutritional deficiency
- Hemolysis
- Chemotherapy/radiation therapy



Etiologies of Nursing Home Anemia

The most common diagnosis was:

- anemia of chronic disease (65.6%),
- followed by anemia of chronic renal failure (13.2%)
- anemia primarily due to iron, vitamin B12 or folate deficiency was found to be only 4%.
- In 15.9% of these cases the main cause of anemia could not be resolved.

Chernetsky A, et alHarefuah. 2002 Jul;141(7):591-4, 667

Underlying Causes of Anemia of Chronic Disease

Associated Diseases	Estimated Prevalence * *percent*
Infections (acute and Chronic)	
Viral / HIV	18-95
Bacterial	
Parasitic	
Fungal	
Cancer †	30-77
Hematologic	
Solid tumor	
Autoimmune	8-71
RA	
SLE/ CTD	
Vasculitis	
Sarcoidosis	
IBD	
Chronic rejection after transplantation	8-70
Chronic kidney disease and inflammation	23-50

• Values shown are ranges. Epidemiologic data are not available for all conditions associated with the anemia of chronic disease. The prevalence and severity of anemia are correlated with stage of underlying condition and appear to increase with advanced age.

† The prevalence of anemia in patients with cancer is affected by therapeutic procedures and age. A high prevalence was reported in one study in which 77 percent of elderly men and 68 percent of elderly women with cancer were anemic. In another study, anemia was observed in 41 percent of patients with solid tumors before radio-therapy and in 54 percent thereafter.

Weiss G, Goodnough LT. *N Engl J Med*. 2005; 352:10: 1011-23

Prevalence of Anemia in the U.S. Population

Data from the Third National Health and Nutrition Examination Survey (NHANES III)

NHANES III Survey

- The National Health and Nutrition Examination Survey [NHANES] is a population-based survey conducted by the National Center for Health Statistics to collect health and nutrition information on the U.S. population
- NHANES III is the most recent survey with publicly available data
  - 33,994 persons surveyed between 1988-1994
  - Designed to obtain nationally representative information

NHANES III Definitions

Condition	Measure	Criteria
Iron deficiency	Serum ferritin ng/ml	<15 ng/ml
Vitamin B_{12} deficiency*	Serum B_{12} pg/ml	<200 pg/ml
Folate deficiency	RBC folate ng/ml Serum Folate ng/ml	<102.6 (MEC only) <2.6 (home only)

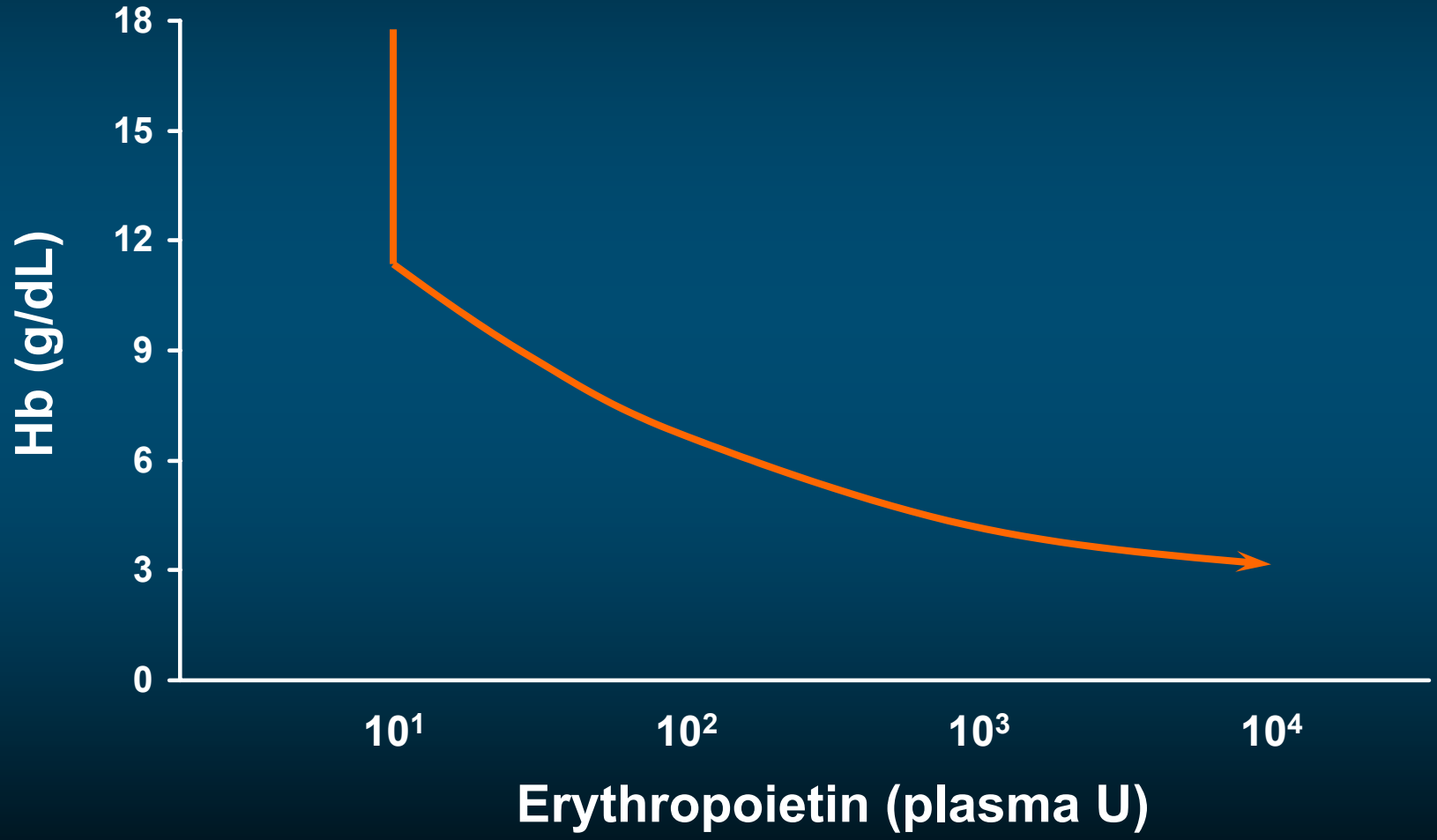
*Serum B_{12} not available in phase I of NHANES III

Distribution of Types of Anemia in Persons Age 50+

Type of Anemia	Est. U.S. Population	% Anemic, Age 50+
Iron deficiency only: Folate deficiency only: B12 deficiency only:	323,698 238,385 176,490	7.3% 5.4% 4.0%
Folate and B12 deficiencies:	59,806	1.3%
Iron with folate and/or B12 deficiencies:	100,697	2.3%
None of the above:	3,539,007	79.7%

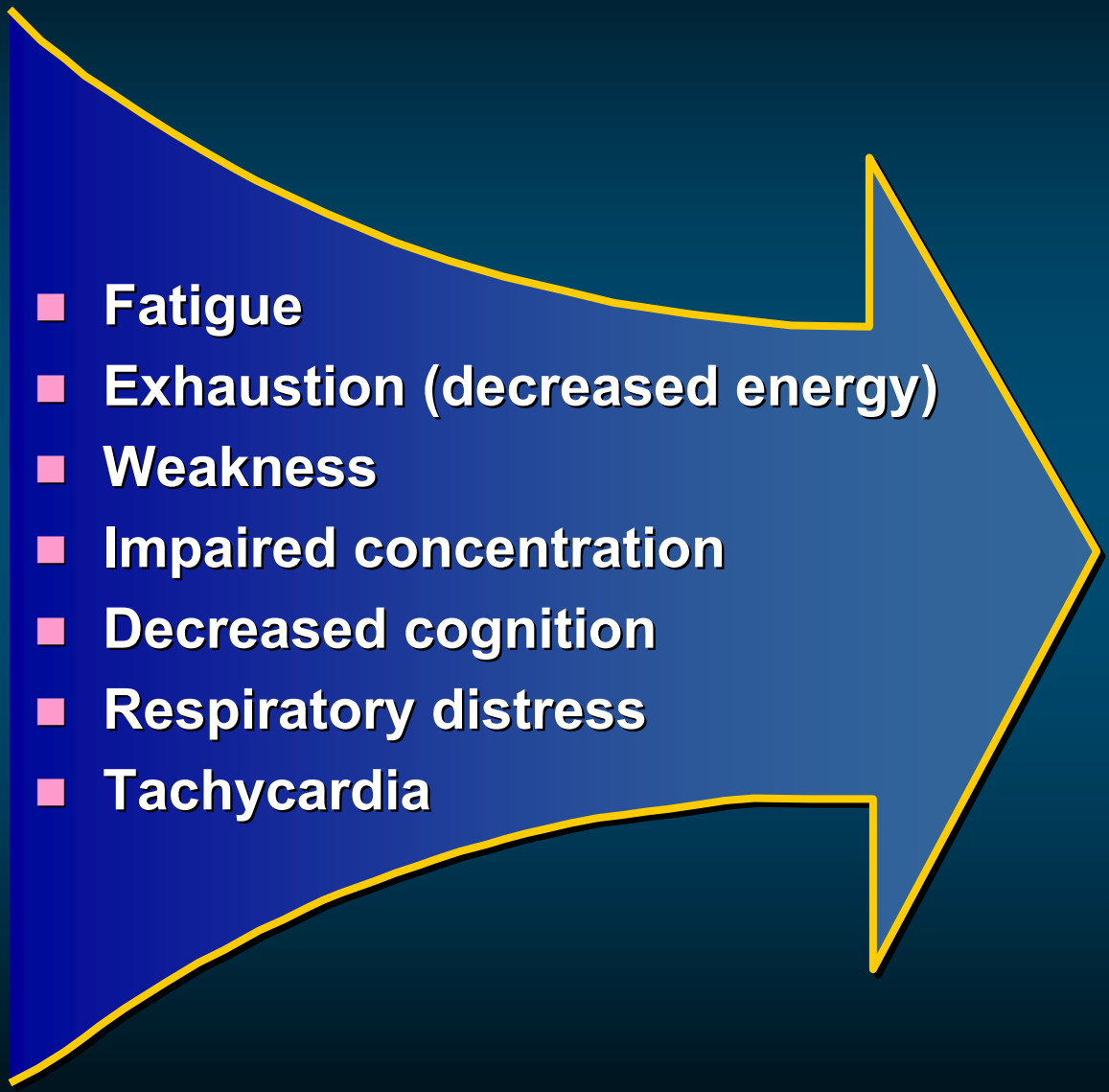
Source: NHANES III, MEC + home exam population, Phase II only; excludes persons with null/blank Hb values

Normal Erythropoietin Production and Hemoglobin Levels



Adapted from Hillman RS, Finch CA, eds. *Red Cell Manual*. 6th ed. 1992:1-38.

Anemia: Symptoms



- Fatigue
- Exhaustion (decreased energy)
- Weakness
- Impaired concentration
- Decreased cognition
- Respiratory distress
- Tachycardia

Leads to

- Impaired quality of life
- Diminished physical capacity

Do You Have Tired Blood?

Ludwig and Strasser. *Semin Oncol*. 2001;28(suppl 8):7-14.

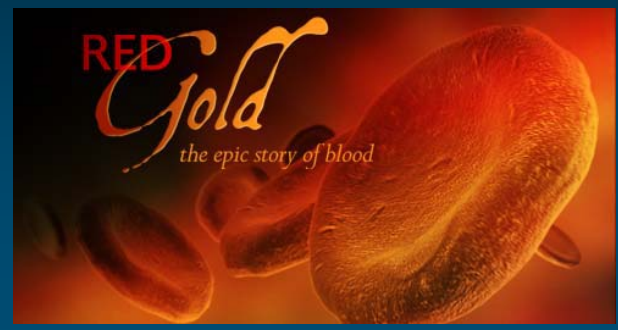
Consequences of Geriatric Anemia

associated with:

- increased mortality
- poor health
- fatigue
- functional dependence
- falls
- can lead to cardiovascular and neurological complications

- Lipschitz D, J Am Geriatr Soc. 2003 Mar;51(3 Suppl):S10-3

Anemia, Cancer, and Cognitive Impairment

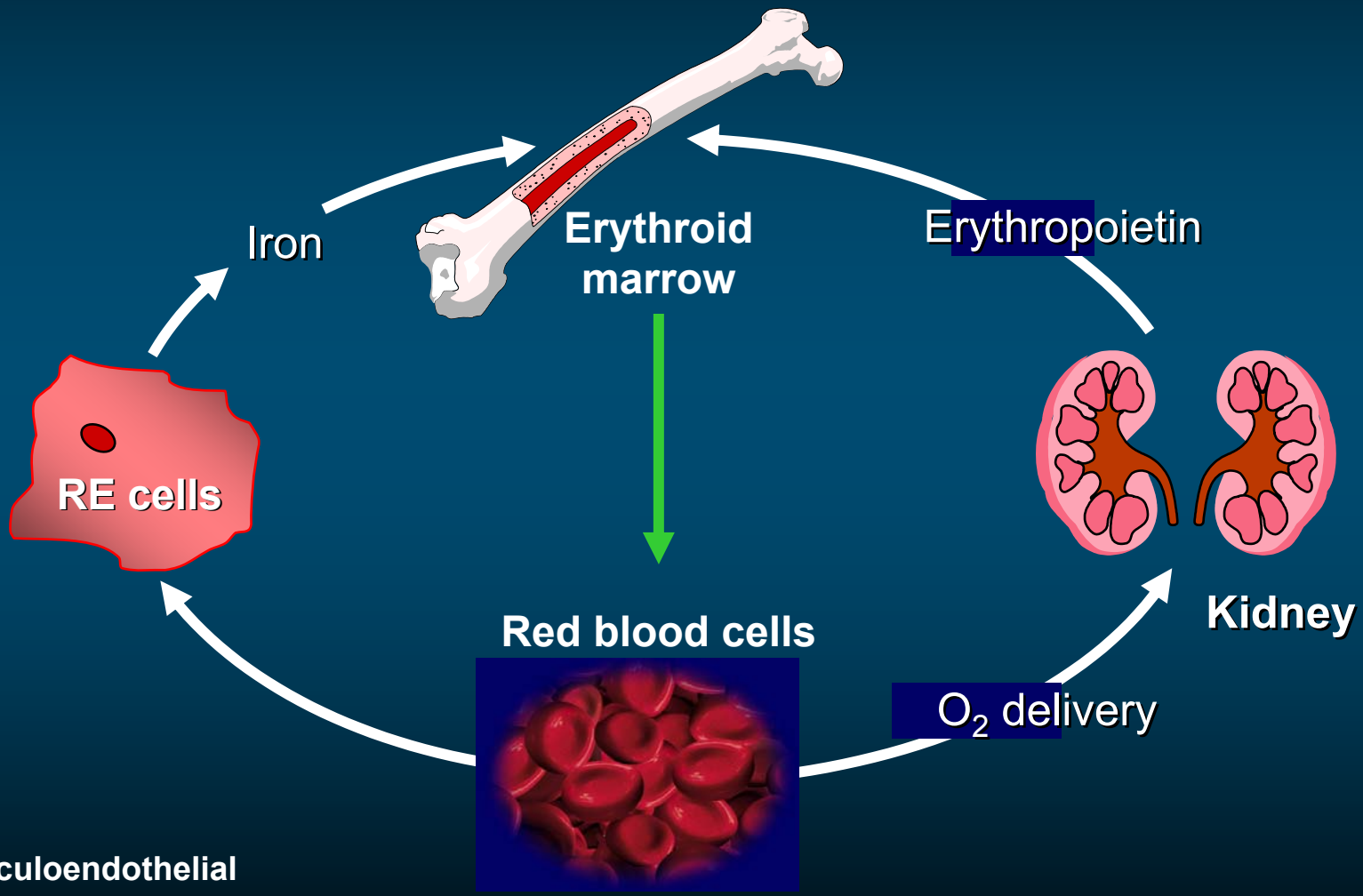


- Anemia affects the young and elderly alike
- Cancer and cancer treatment cause anemia and have been linked to cognitive impairment
- Anemia can exacerbate cognitive deficits, particularly in the elderly

http://www.pbs.org/wnet/redgold/basics/ancient.htmlhttp://www.pbs.org/wnet/redgold/basics/ancient.html

Beard CM, et al. *Ann Epidemiol.* 1997;7:219-224.
Milward EA, et al. *Neuroreport*. 1999;10:2377-2381.

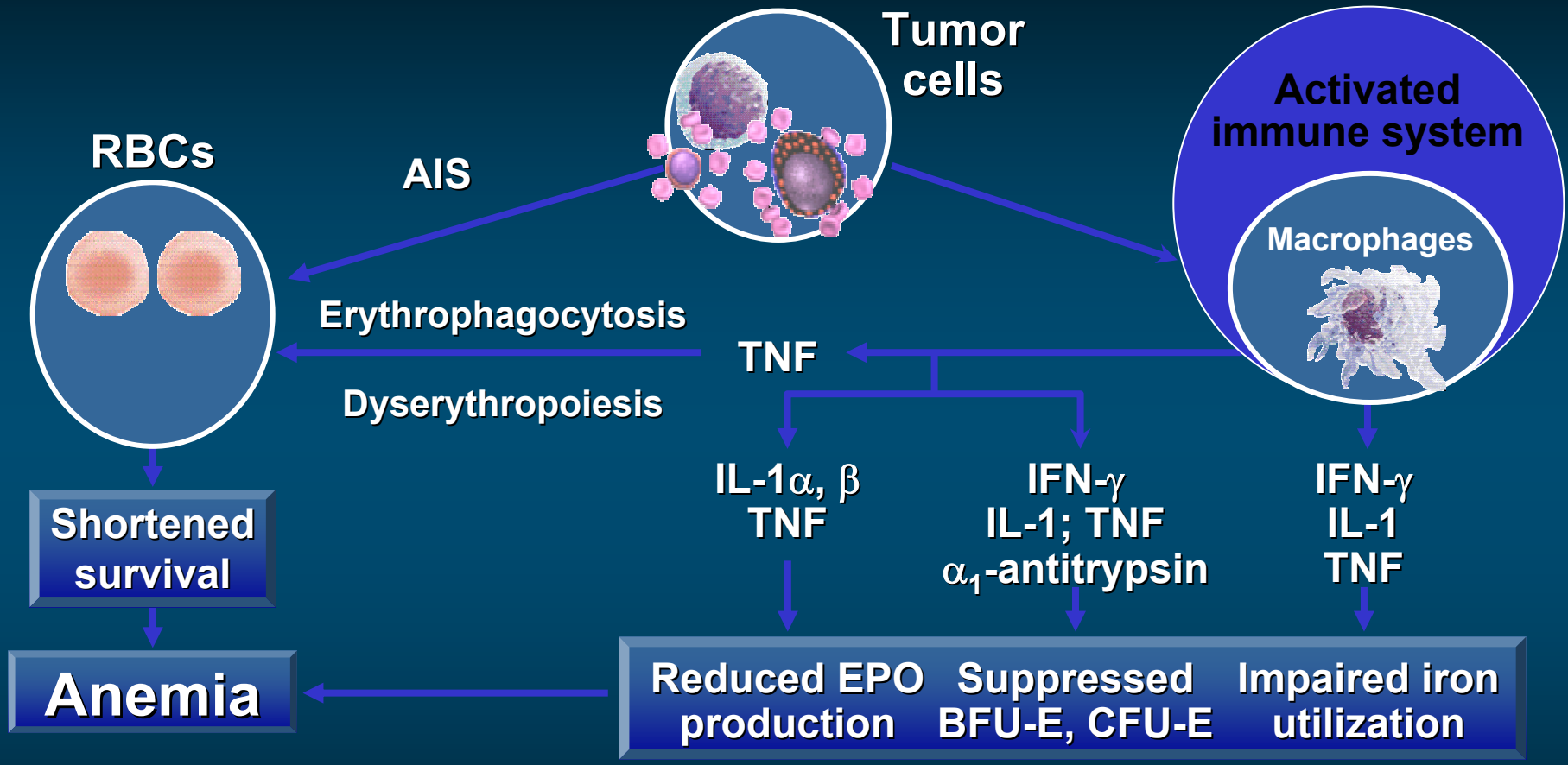
Normal Erythropoiesis



RE = reticuloendothelial

Hillman RS. In: Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine.* 1998:334-339.

Anemia: Cancer-Related Inflammatory Mechanism



AIS=anemia-inducing substance; TNF=tumor necrosis factor; EPO=erythropoietin; BFU-E=burst-forming unit erythroblasts; CFU-E=colony-forming unit erythroblasts.

Nowrousian et al. In: *rhErythropoietin in Cancer Supportive Treatment*. 1996:13-34.

Anemia of Chronic Disease

- Inflammation, neoplasia
- Blunted erythropoietin response
- Impaired iron utilization
  - Bone marrow stores adequate
  - Low serum iron

Ludwig H, Fritz E. *Semin Oncol.* 1998;25(3 Suppl 7):2-6.

Differentiating IDA from ACD

- Serum ferritin level
- Soluble transferrin receptor level

Soluble transferrin receptor and soluble transferrin receptor-ferritin index for evaluation of the iron status in elderly patients

Genc S et al,Tohoku J Exp Med. 2004 Feb;202(2):135-42

Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia

Variable	ACD	FE (-)	Both
Iron	↓	↓	↓
Transferrin	↓ / ↔	↑	↓
Transferrin saturation	↓	↓	↓
Ferritin	↔ / ↑	↓	↓ / ↔
Soluble transferrin receptor	↔	↑	↔ / ↑
Ratio of soluble transferrin receptor to Log ferritin	↓	↑	↑
Cytokine levels	↑	↔	↑

Weiss G, Goodnough LT. *N Engl J Med.* 2005; 352:10: 1011-23

*

Pathophysiologic Factors in Anemia of Chronic Disease.

- Pathologic Iron Homeostasis
- Impaired Erythropoiesis
- Blunted Erythropoietin Response

Pathologic Iron Homeostasis

Key Factors	Mechanisms	Systemic Effects
TNF-α or IL-1	Induces ferritin transcription	Hypoferremia,
	Leads to a decreased erythrocyte half-life, mediated by TNF-α	hyperferritinemia
		Erythrophagocytosis
IL-6	Induces ferritin transcription or translation	Hypoferremia, hyperferritinemia
	Stimulate formation of hepcidin	Hypoferremia
INF-γ or LPS	Stimulates DMT1 synthesis; down-regulates ferroportin 1 expression	Hypoferremia
IL-10	Induces transferrin-receptor expression; stimulates ferritin translation	Hypoferremia, hyperferitinemia
Erythrophagocytosis	Reduces erythrocyte half-life through increased uptake of erythrocytes damaged by TNF-α	Hypoferremia, anemia

DMT1 denotes divalent metal transporter 1, LPS lipopolysaccharide

Weiss G, Goodnough LT. *N Engl J Med*. 2005; 352:10: 1011-23

Impaired Erythropoiesis

Key Factors	Mechanisms	Systemic Effects
INF-γ, IL-1 or TNF-α	Inhibits proliferation and differentiation of CFU-E and BFU-E	Anemia with normal or decreased reticulocyte counts
	Causes hypoferremia through diversion of iron to the RES	Anemia with increased levels of ti protoporphyrin
	Induces formation of nitric oxide	Anemia with increase levels of levulinic acid
α-1-antitrypsin	Limits iron uptake by erythroid cells	Anemia
Tumor cells or microbes	Infiltrate bone marrow	Anemia, pancytopenia or both
	Produce soluble mediators	Anemia, pancytopenia of both
	Consume vitamins	Systemic deficiency of folate or cobalamin
Hypoferremia	Caused by cytokine-mediated diversion of iron into the RES and reduced iron absorption	Anemia

RES denotes reticuloendothelial system

Weiss G, Goodnough LT. *N Engl J Med*. 2005; 352:10: 1011-23

Blunted Erythropoietin Response

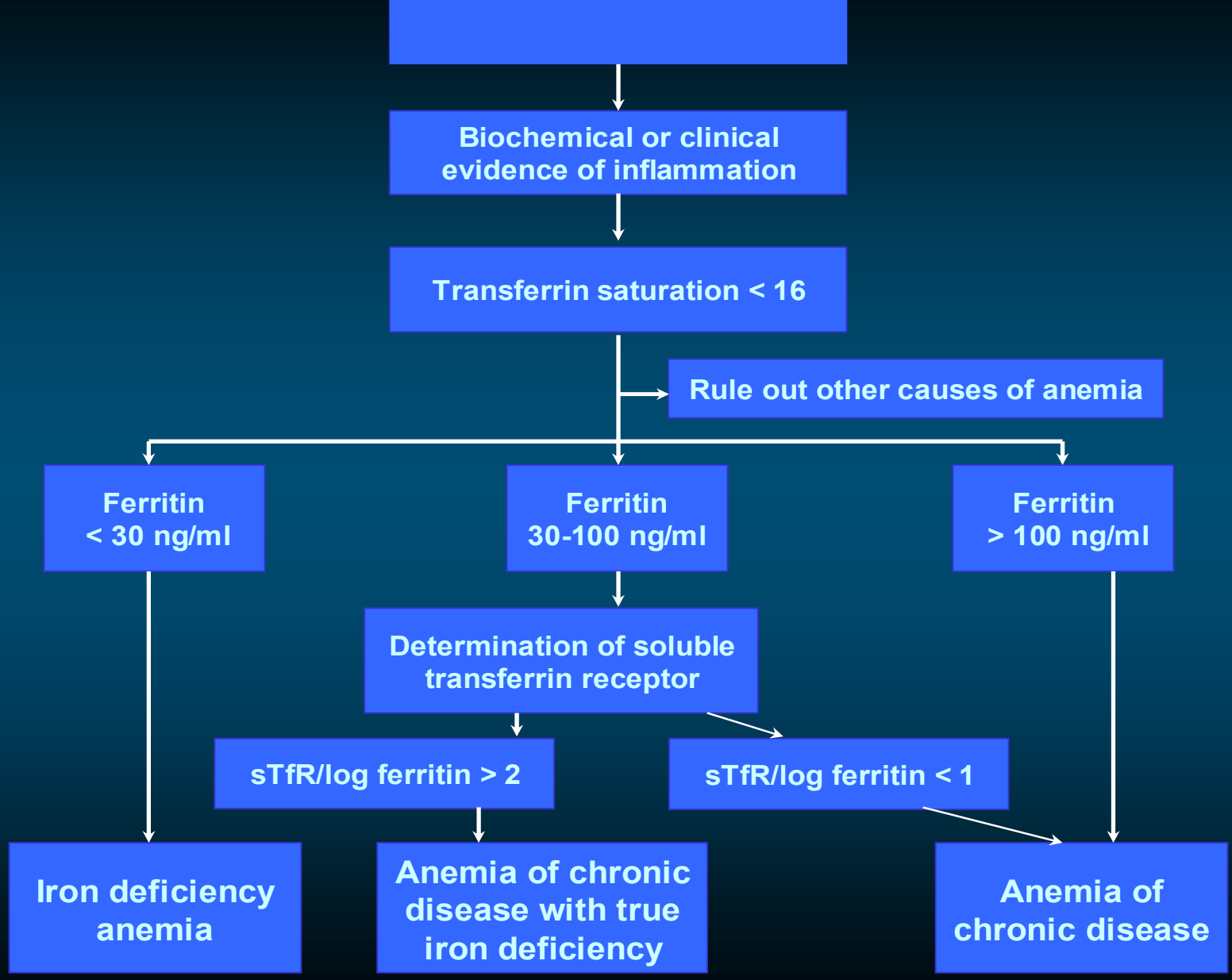
Key Factors	Mechanisms	Systemic Effects
Erythropoietin deficiency	Inhibits erythropoietin production by IL-1 and TNF-α	Decreased levels of circulating erythropoietin
Hypoferremia	Reduces erythropoietin responsiveness of progenitor cells owing to iron restriction	Anemia, hypoferremia
INF-γ, IL-1, & TNF-α	Impair responsiveness of progenitor cells to erythropoietin	Anemia

Weiss G, Goodnough LT. *N Engl J Med*. 2005; 352:10: 1011-23

Geriatric-Related Anemias: Initial Evaluation

- Patient should be assessed for deficiencies
  - Iron (total iron-binding capacity, serum iron, ferritin)
  - Folate (serum homocysteine)
  - Vitamin B_{12} (serum methylmalonic acid)
  - R/O renal insufficiency
- Treatment must be individualized
  - Correct nutritional and metabolic deficiencies
  - Treat underlying infections or inflammatory processes
  - R/O MDS
  - Manage hemolytic diseases, occult blood loss

NCCN. Available at: www.nccn.org.



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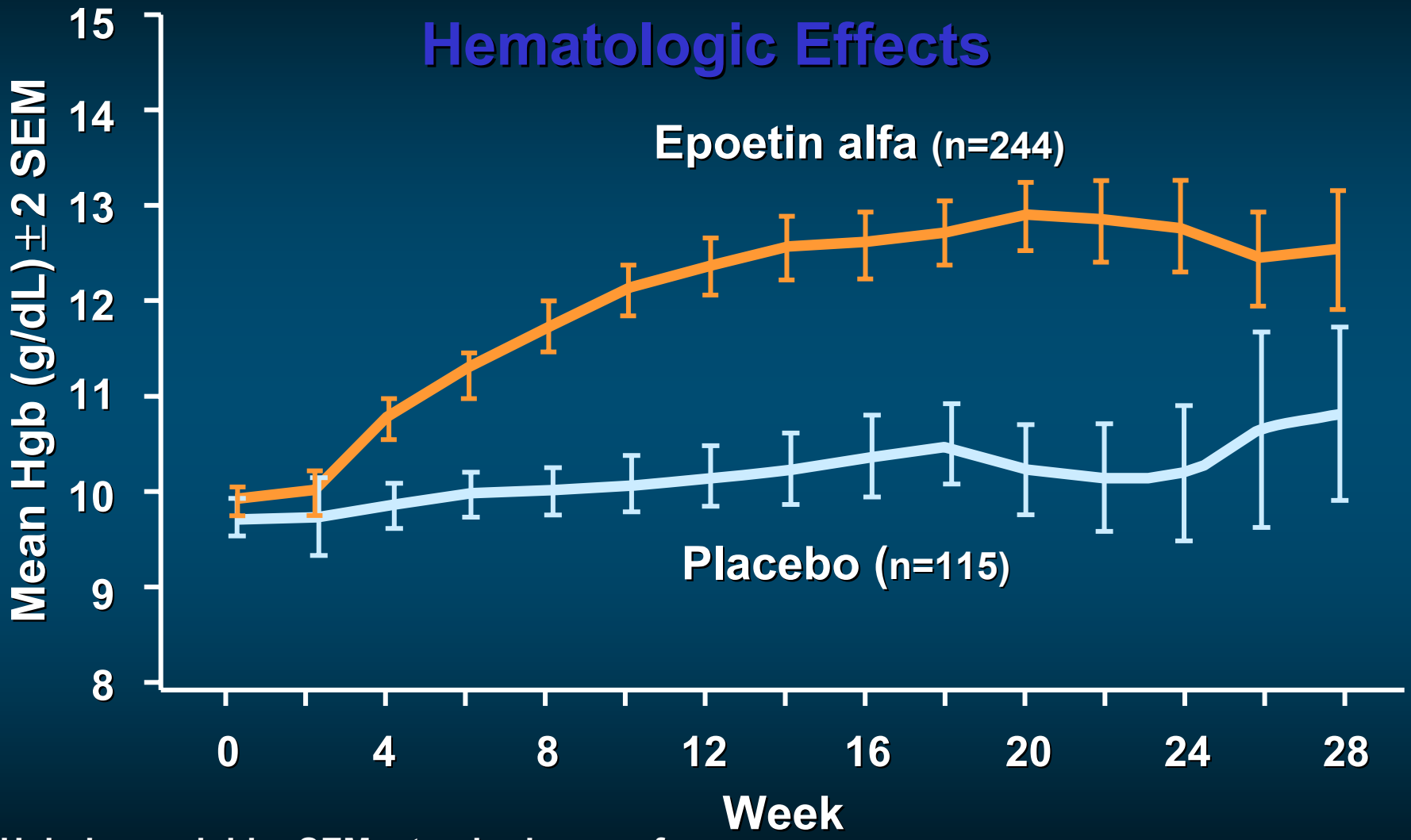
Randomized Placebo-Controlled Trial



Hgb=hemoglobin; SEM=standard error of mean.

Littlewood et al. *J Clin Oncol.* 2001;19:2865-2874. Courtesy of Lippincott Williams & Wilkins http://www.lww.com.

Recombinant Human Erythropoietin: Indications in Cancer

- Anemia in cancer patients on chemotherapy
  - For treatment of anemia in nonmyeloid malignancies when the anemia is caused by chemotherapy
  - To decrease the need for transfusions in patients who will receive concomitant chemotherapy for a minimum of 2 months
- Not indicated for treatment of anemia caused by iron or folate deficiencies, hemolysis, or gastrointestinal bleeding

Epogen® [package insert]. 1999.
Procrit® [package insert]. 2000.

rHuEPO Treatment: Summary of Potential Benefits

- Increased hemoglobin concentrations
- Reduced need for transfusions
- Fewer adverse effects
- Outpatient treatment possible
- Improved quality of life
- Improved survival rate?

rHuEPO=recombinant human erythropoietin.

Littlewood et al. *J Clin Oncol*. 2001;19:2865-2874.
Ludwig and Fritz. *Semin Oncol*. 1998;25(suppl 7):2-6.

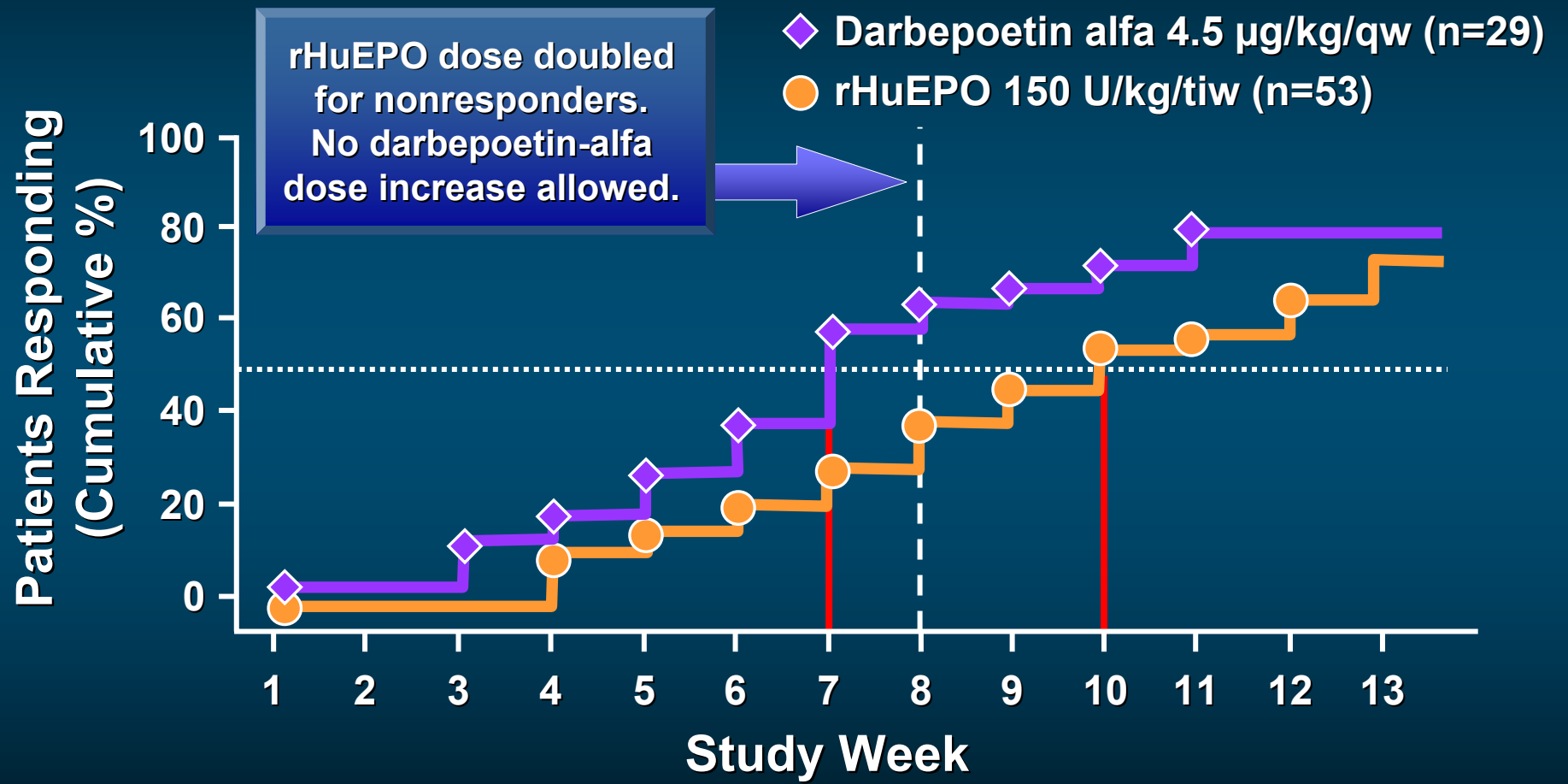
rHuEPO Treatment: Caveats and Drawbacks

- Effective in only 50% to 60% of patients
- Slow time to response
- Frequent injections – inconvenience
- Patient compliance
- Suboptimal response to rHuEPO may be related to iron deficiency and other factors
- Cost can be significant

rHuEPO=recombinant human erythropoietin.

Demetri. *Br J Cancer*. 2001;84(suppl 1):31-37.

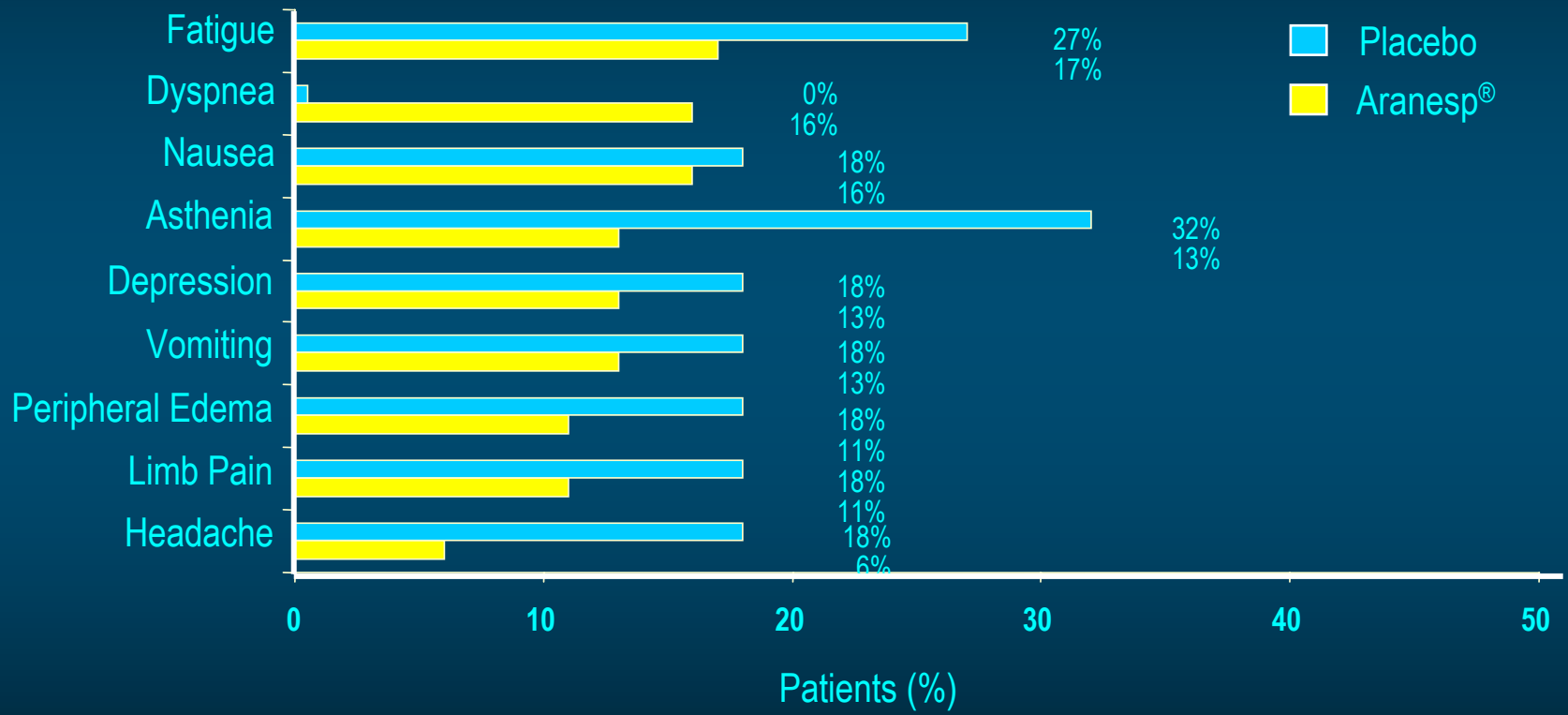
Darbepoetin Alfa vs rHuEPO: Time to Hgb Response



95% confidence intervals for cumulative percentage of patients responding by week 13. Kaplan-Meier proportions; rHuEPO=recombinant human erythropoietin; Hgb=hemoglobin.

Glaspy et al. *Proc & poster ASCO 2001*.

Aranesp® (darbepoetin alfa) in Anemia of Cancer: Summary of Safety



- Adverse events similar to those observed in cancer patients

- No safety issues associated with less frequent dosing
- No evidence of antibody formation to darbepoetin alfa
- Aranesp® was well tolerated beyond 12 weeks of treatment

Smith R et al. *Br J Cancer.* 2003;88:1851-1858.

Aranesp® (darbepoetin alfa) in Anemia of Cancer: Summary of Efficacy

- Q4W Dosing
- Hematopoietic response in up to 70% of patients
- Mean change in Hb at 6.75 mcg/kg Q4W dose of Aranesp®
  - 1.22 using the ITT approach
  - 1.38 g/dL using the completers' analysis
- RBC transfusion rates for 6%-16%, compared with 21% for placebo group

Smith R et al. *Br J Cancer.* 2003;88:1851-1858.

Aranesp™ (darbepoetin alfa) Chemotherapy-Induced Anemia

- Aranesp™ is contraindicated in patients with uncontrolled hypertension. Erythropoietic therapies may increase the risk of thrombotic and other serious events; dose reductions are recommended if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period
- The most commonly reported side effects in Aranesp™ trials were fatigue, edema, nausea, vomiting, diarrhea, fever, and dyspenea; no important differences were observed between Aranesp™ and Epoetin alfa

Amgen Inc. Aranesp™ (darbepoetin alfa) [prescribing information]. Thousand Oaks, CA; 2002.

Summary

- Anemia is prevalent in geriatric patients with cancer as a result of:
  - Chemotherapy and radiation treatments
  - Chronic disease
- The impact of anemia has been underappreciated
  - Association between anemia and quality of life is well established
  - Potential impact upon outcomes
- Weekly dosing of epoetin alfa significantly improves Hb and quality of life
- Every other week Darbopoietin dosing more convenient
- The association between anemia, cognitive function, and survival is still being explored

Geriatric-Related Anemia: Effects of Erythropoietin

- ↑ Hemoglobin ($p<0.001$)
- ↓ Transfusions ($p=0.0057$)
- ↑ Quality of life ($p<0.01$)

Littlewood et al. *J Clin Oncol*. 2001;19:2865-2874.