

ESA UPDATE AND USE IN CANCER PATIENTS

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Anemia in Malignancy

- Most commonly due to patient's antineoplastic agents
 - May be presenting sign of malignancy
- Frequent cause of fatigue
 - Most common complaint of cancer patients, therefore important to intervene to improve patient's quality of life

Anemia in Malignancy

■ Etiology

- Multiple factors may contribute, therefore important to correlate patient's history and physical as well as laboratory findings

Anemia in Malignancy

- In malignancy, other causes:
 - Direct effects of the neoplasm
 - An effect of the product of the neoplasm
 - Effects of treatment of the neoplasm

Anemia in Malignancy

■ Direct Effects of the Neoplasm

– External bleeding

■ Intraluminal neoplasms

- Evaluation should include stool/urine samples for blood
- Iron studies c/w iron deficiency anemia (blood loss for men >1200 mL, women > 600 mL)

– Impaired iron absorption

- Often in patients whose malignancy involve sites of maximal iron absorption, i.e. mucosa of the jejunum or duodenum

Anemia in Malignancy

■ Direct Effects of the Neoplasm

– Internal bleeding

- Occasionally there is significant bleeding into the body of the neoplasm
 - Most commonly seen in HCC, but also seen in liver metastases, stromal ovarian tumors, and retroperitoneal tumors

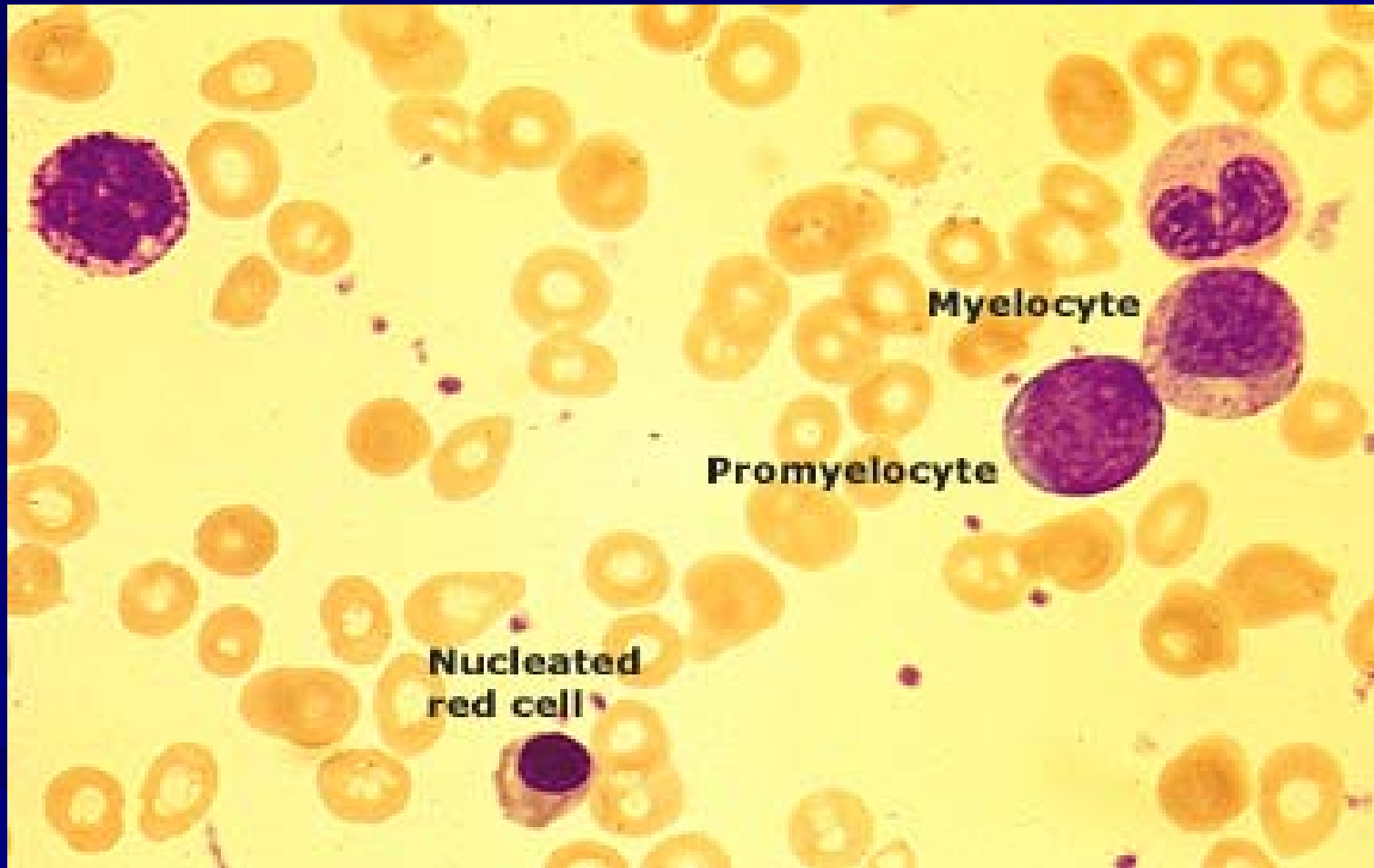
– Hemophagocytosis

- Seen most commonly in leukemia/lymphoma
 - Characterized by ingestion of RBC's from by macrophages or cancer cells

Anemia in Malignancy

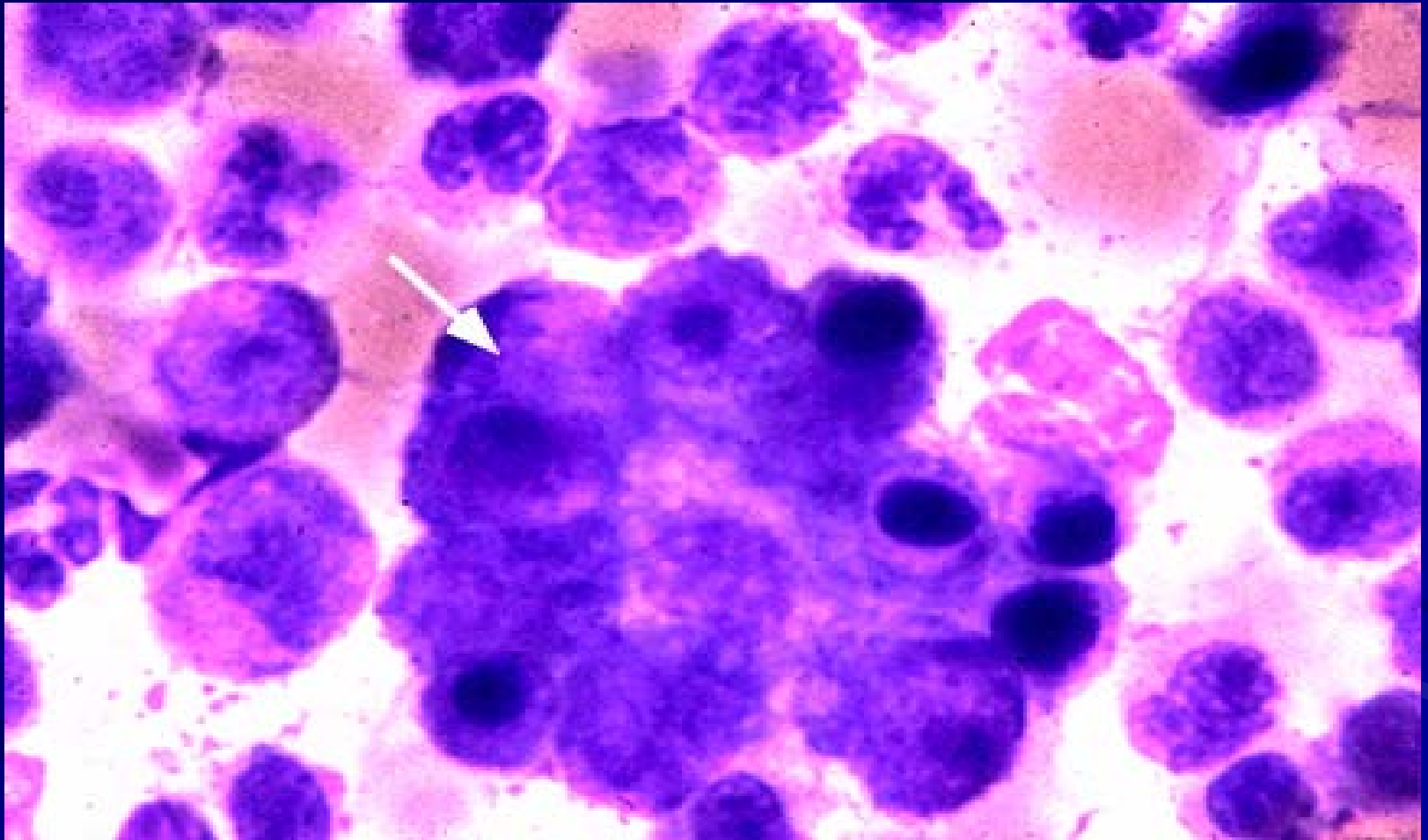
- Direct Effects of the Neoplasm
 - Bone marrow replacement
 - Seen in leukemia, lymphoma, plasma cell dyscrasias, and solid tumors that are metastatic to the bone marrow
 - Finding of a leukoerythroblastic picture on peripheral blood smear

Leukoerythroblastic Reaction



Characterized by the appearance of immature granulocytes, tear drop RBC's, and nucleated RBC's

Bone marrow replacement by tumor



Clump of tumor cells in the bone marrow

Anemia in Malignancy

■ Anemia from the products of neoplasm

– Hemolysis

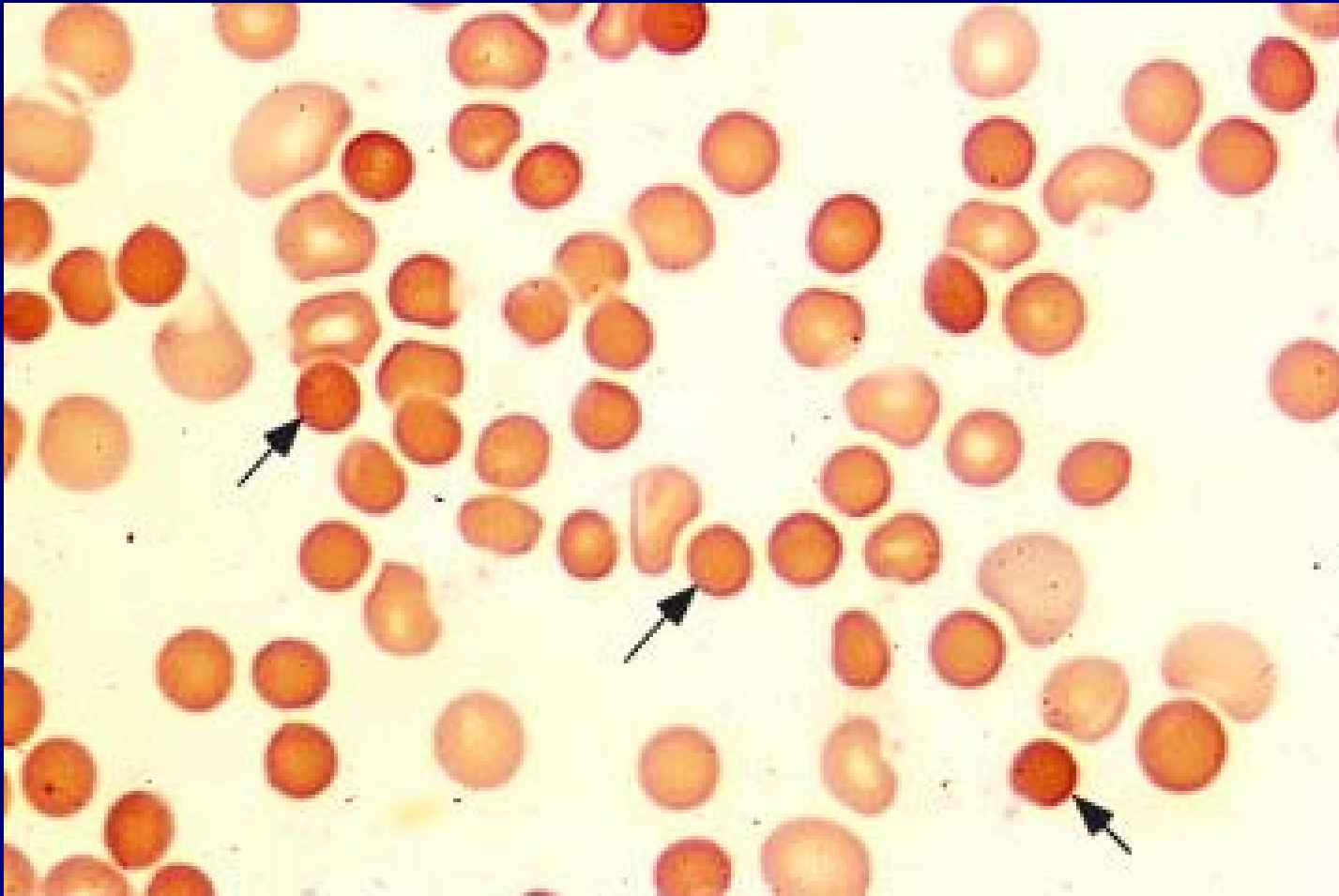
- Production of autoantibodies that recognize red cell membrane antigens resulting in an autoimmune hemolytic anemia
- Microangiopathic changes, causing fragmentation hemolysis

Anemia in Malignancy

■ Autoimmune hemolytic anemia

- Associated with IgG or C3d on circulating RBC's (detected by Coombs' test)
- Hallmark finding of spherocytes on peripheral smear
- Increased LDH, decreased haptoglobin
- Seen most commonly in NHL, HL, AML, ALL, CLL, MDS, some carcinomas
- May be also caused by certain treatments, i.e. fludarabine for CLL

Spherocytosis in AIHA



Anemia in Malignancy

- Autoimmune hemolytic anemia
 - Treatment is usually directed at treating the underlying malignancy

Anemia in Malignancy

- Microangiopathic hemolysis
 - Coombs' negative, schistocytes on blood smear
 - May consequence of DIC (usually plentiful platelets) or TTP-HUS (decreased platelets)

Anemia in Malignancy

■ Microangiopathic Hemolytic Anemia

– DIC

- APML, mucinous adenocarcinomas (gastric, breast, pancreas, prostate, lung)

- Due to activator Factor VII on tumor cells, in addition to secretion of cytokines
- Cancer procoagulant activates pathways as well

– TTP-HUS

- May be due to anti-neoplastic agents

- Mitomycin-C, Bleo/Cisplatin combinations, and radiation and high dose chemotherapy

Anemia in Malignancy

- **Microangiopathic hemolytic anemia**
 - Management focuses on treatment of the underlying disease
 - May need to use agents such as heparin to minimize thrombotic complications
 - May also need to use blood products, such as FFP/cryo/platelets for bleeding complications in DIC

Anemia in Malignancy

- Anemia from products of neoplasm
 - Inflammation
 - Due to cytokines produced by malignancy
 - IFN-a, IFN-b, IFN-g, TGF-b, IL-1, IL-6
 - Results in block of iron utilization, inhibiting mRNA synthesis, and exerts ill-defined suppressive effects on erythropoiesis
 - Diagnosis made by exclusion

Anemia in Malignancy

- Anemia of chronic inflammation
 - RBC- normocytic, normochromic
 - Abundant iron stores in the marrow, and low serum erythropoietin levels
 - Low iron and TIBC, with elevated ferritin

Anemia in Malignancy

■ Anemia due to cancer treatment

- Most common reason for anemia

- Mechanisms

- Stem cell death with long-term myelosuppression following chemo with non-cell cycle dependent drugs, e.g. alkylating agents

- Long term myelodysplasia

- *Alkylating agents and topoisomerase II inhibitors*

- Non-myeloablative doses of chemotherapy agents are active against actively proliferating cells

- May worsen as treatment courses increase in number

Anemia in Malignancy

■ Mechanisms

- Suppression of erythropoietin
- Oxidant damage to mature hematopoietic cells
- Induction of immune-mediated cell destruction
- Exacerbation of underlying AIHA (fludarabine)
- Exacerbation of MAHA (mitomycin-C)

Anemia in Malignancy

- Multifactorial reasons
- Common complication
- Linked to poorer prognosis as adequate tissue oxygen levels are required for cytotoxicity
 - Can also reduce quality of life
- Important to determine all possible causes, i.e. B12 deficiency to appropriately treat patient

Treatment options

- Transfusion: almost always effective, exceptions are....
- *Erythropoietin and darbopoietin (ESA)*
 - Making the choice
 - How quickly you need to raise hemoglobin
 - Risk of iron overload in transfusion
 - Cost
 - Patient preference

	PRBC	ESA
Response	Immediate	Delayed for weeks
Risk of iron overload	Yes	No
Infectious risk	Yes, but less nowadays	No
Access issues	Yes	Not an issue
Cost	\$	\$\$\$\$\$\$\$\$
Religious beliefs	Issue	Not an issue

ESAs & HEMATOLOGIC MALIGNANCIES

- MDS
- CLL
- MM

ESA & MDS

- EPO concentrations are generally inversely related to the degree of anemia in patients with MDS
- Highest values being seen in patients with erythroid hypoplasia
- Serum EPO may be suboptimally elevated in MDS patients relative to the degree of anemia.
- Recombinant human EPO therapy has been instituted in an attempt to correct the hypoproliferative anemia

ESA & MDS

- 20-55 % of patients with MDS respond to treatment with EPO, usually at relatively high doses
- Responses seen with epo level <100
- Can be delayed up to 26 weeks
- Higher RR for epo <150 and good karyotype MDS

ESA

■ Efficacy

- First established in renal failure patients on dialysis
- Numerous studies establishing efficacy in cancer patients, primary parameter was decreasing number of RBC transfusions
 - Meta-analysis (JNCI 2006;98:708)
 - Summarized 57 trials, 9353 patients randomized to management with ESA +/- RBC transfusions vs. RBC transfusions alone
 - ESA sig. reduced the number of RBC transfusions
 - One unit less on average
 - NNT = 6

ESA

■ Efficacy

- If baseline <12 , ESA increased the likelihood of obtaining response (>2 g/dL)
- Increased risk of thromboembolic complications
- Increased risk of hypertension
- Overall positive effect on quality of life, most pronounced in patients with severe anemia

ESA

- Some controversial issues
 - Effect of ESA 's on disease control and survival
 - Role of erythropoietin receptors in stimulating tumor growth
 - Appropriate hemoglobin levels at which to initiate ESA therapy and the hemoglobin target

ESA

- Effect on disease control and survival
 - Presence of anemia has been linked to shortened survival
 - Attributed in part to a poorer response to anticancer treatments dependent upon oxygen delivery for their cytotoxicity
 - Supported by some observational studies suggesting that raising hemoglobin >12 or 14.5 improved survival in NSCLC or head and neck cancer, respectively

ESA

■ Negative studies

– Head and neck cancer

■ Directly evaluated in three RCT

– Goal hgb in women, 12-14 and men, 15-16 both before and during curative RT in Stage III/IV patients

■ All three trials had worse outcomes in the patients treated with ESA ? Tumor stimulatory effect?

ESA

■ Breast cancer- BEST trial

- 939 women w met. breast cancer, randomized to receive epoetin alpha vs. placebo to maintain hgb 12-14.
 - Study terminated early due to increased mortality in the treated arm. 1 year OS decreased for patients treated (70 vs. 76%)

ESA

- Results of the head and neck trials and BEST trial resulted in an FDA issued black box warning in March of 2007
 - MD's are urged to limit ESA use to patients with chemotherapy-induced anemia and to use the lowest doses that will gradually increase the hemoglobin to the lowest level (no higher than 12)

ESA

- RCT of patients with SCLC treated with darbopoietin for a maximum of hgb of 13 showed no difference in survival, and decreased transfusion requirements.

ESA

■ Erythropoietin receptors

- May be mechanism for more rapid disease progression and shortened survival following treatment with ESA
 - A number of tumors have been shown to possess cell surface EPO-R's
 - ?promote angiogenesis, tumor growth, and/or survival of tumor cells
 - Head and neck cancer patients receiving RT- given epoetin for anemia
 - Tumors + for EPO-R had increased risk of locoregional progression or death

ESA

■ Erythropoietin receptors

- No in vivo tumor growth or angiogenesis seen in a study using rodent with four different tumor types expressing EPO-R
- Available antibodies to the EPO-R may actually be staining non-specific antigens also

Target Hemoglobin

- *When used in renal patients, higher levels correlated with increase in thrombotic and vascular events*
 - Similar relationship in cancer patients
 - Data is not as convincing, but supports theory
 - Meta-analysis with 1413 cancer patients
 - Patients treated with epo-beta vs. placebo
 - Mean hemoglobin was 12.6
 - Trend towards increased thromboembolic rates, although not statistically significant

Target Hemoglobin

- Optimal threshold has not been established
 - Guidelines suggest initial Hgb level 10g/dL or less, or if patients are symptomatic with level 10-11.
 - Target hemoglobin 11-12

Patient Selection

- Correctable cause should be identified prior to starting the ESA
 - Rule out other causes of anemia, other than chemotherapy-induced.

ESA

- Variable patient responses
 - Not all patients benefit from ESA
 - 15-20% still require RBC transfusions
 - 50-70% have a hgb increment of >1 g/dL after 8-12 weeks of therapy

ESA

- Lack of hemoglobin response
 - Extensive involvement of the bone marrow with malignancy, resulting in insufficient elements to respond to the ESA
 - Pts with increased endogenous erythropoietin levels (>500)
 - Erythropoiesis-inhibiting cytokines, seen in anemia of chronic disease
 - Insufficient iron stores- may need to supplement during treatment

Iron

- Availability of iron can limit the Hgb response following treatment with erythropoietins
 - May be secondary to iron deficiency or deficiency in iron mobilization, due to cytokine-mediated inhibition of iron transfer
 - Supplemental iron can be given to maintain an iron saturation of >20% and a serum ferritin >100
 - Better seen with parenteral iron formulations

ESA Formulations

■ Epoetin alfa

- Should see a rise in Hgb between 8-12 weeks
 - Weekly dosing
 - 30,000 to 40,000 U weekly SQ
 - Similar to TIW dosing
 - Every 2 weeks dosing
 - 80,000 U given Q2 weeks similar to patients being treated with 40,000 U once a week
 - Every 3 weeks studied with 120,000 U given- all parameters equal to 40,000 U weekly, but there was a lower hemoglobin noted
- *Not recommended in cancer patients NOT getting chemotherapy*

ESA Formulations

- Darbopoietin
 - Indicated for chemotherapy-induced anemia
 - Has clinical efficacy when given as infrequently as every 3 to 4 weeks
 - Longer half-life than epoetin and has less EPO-R binding activity
 - Double blind trial with 314 pts with hgb < 11 receiving chemo for lung cancer
 - Randomly assigned to receive weekly darbo (initial dose of 2.25ug/kg) or placebo

Darbopoietin

■ Results

- Fewer patients treated with darbopoietin required transfusion during the 1st 28 days
 - Rate of hematologic response was higher in the darbopoietin group
 - More patients showed a >25% improvement in QOL measurement

■ Guidelines

- 200 mcg every 2 weeks
 - Similar to epoetin 40,000 U weekly
- 500 mcg every 3 weeks
- *Also NOT indicated for anemic cancer patients NOT getting concurrent chemotherapy*

Anemia in Malignancy

- Cancer patients not receiving chemo
 - 989 patients with solid tumor NOT on chemotherapy, randomly assigned to receive darbpo 6.75 ug/kg Q4wks vs. placebo
 - Treatment held if hgb > 13, reinstated with a 25% dose reduction once hgb < 12
 - Increase in the number of deaths during study in the treatment arm (49 vs. 46%, HR 1.29)
 - CV and thrombotic events were more frequent in the treatment arm (9.7 vs. 7.7%, SS not published)
- *Preliminary results suggest that ESA may be more harmful in these patients, even though there is widespread off-label usage*

Anemia in Malignancy

- Multicenter double-blind placebo-controlled trial designed to evaluate the impact of epoetin alfa on the QOL of 300 patients with NSCLC that were incurable
 - All patients had cancer-related anemia, not due to systemic treatment
 - Epoetin given 40,000 U weekly for 12 weeks with target hemoglobin not to exceed 14 g/dL
 - Unplanned safety analysis performed after enrollment of first 70 patients because of reports of thrombotic events in other trials
 - Median survival significantly shorter with epoetin treatment (63 vs. 120 days)
 - Patient enrollment was suspended

ASH/ASCO guidelines 2007

- Optimal threshold hemoglobin level for the initiation of ESA therapy and the target hemoglobin level during treatment have not been definitively established.
- ASH/ASCO guidelines for patients with chemotherapy-induced anemia include the following recommendations:
 - The threshold for initiating therapy is a hemoglobin level that is approaching or has fallen below 10 g/dL. Whether to use an ESA in patients with a hemoglobin ≥ 10 g/dL but < 12 g/dL should be determined by clinical circumstances.
 - Treatment with an ESA should be discontinued if there is no response to treatment within six to eight weeks (as evidenced by a rise in hemoglobin of less than 1 to 2 g/dL or no decrease in transfusion requirement).
 - The target hemoglobin level should not exceed 12 g/dL during treatment. Once hemoglobin exceeds 11 g/dL, the dose of ESA should be decreased by 25 percent. If the hemoglobin during treatment exceeds 12 g/dL, therapy should be withheld and reinstated at a lower dose once the hemoglobin falls below 11 g/dL.

Anemia in Malignancy

- FDA and Medicare actions
 - Patients not receiving chemotherapy
 - FDA issued black box safety alert indicating that ESA's offer no benefit and may be harmful
 - Patients receiving chemotherapy- labeling revisions
 - Lowest possible dose of ESA should be used that will gradually increase the Hgb concentration to the lowest level sufficient to avoid transfusions
 - ESA's increased the risk of death and for serious CV events when administered to target Hgb >12

Anemia in Malignancy

■ US FDA

- Released unpublished data from randomized study with 681 non cancer patients undergoing spinal surgery
 - Patients received standard of care +/- epoetin alfa for reduction of blood transfusions
 - Patients did not receive prophylactic anticoagulation, and there was a higher incidence of DVT in group receiving epoetin alfa

Anemia in Malignancy

- Medicare

- *In March 2007, an instruction was issued to local carriers that it would prohibit Medicare coverage of the drugs when used for anemia in cancer patients NOT being treated with chemotherapy*

Thank You