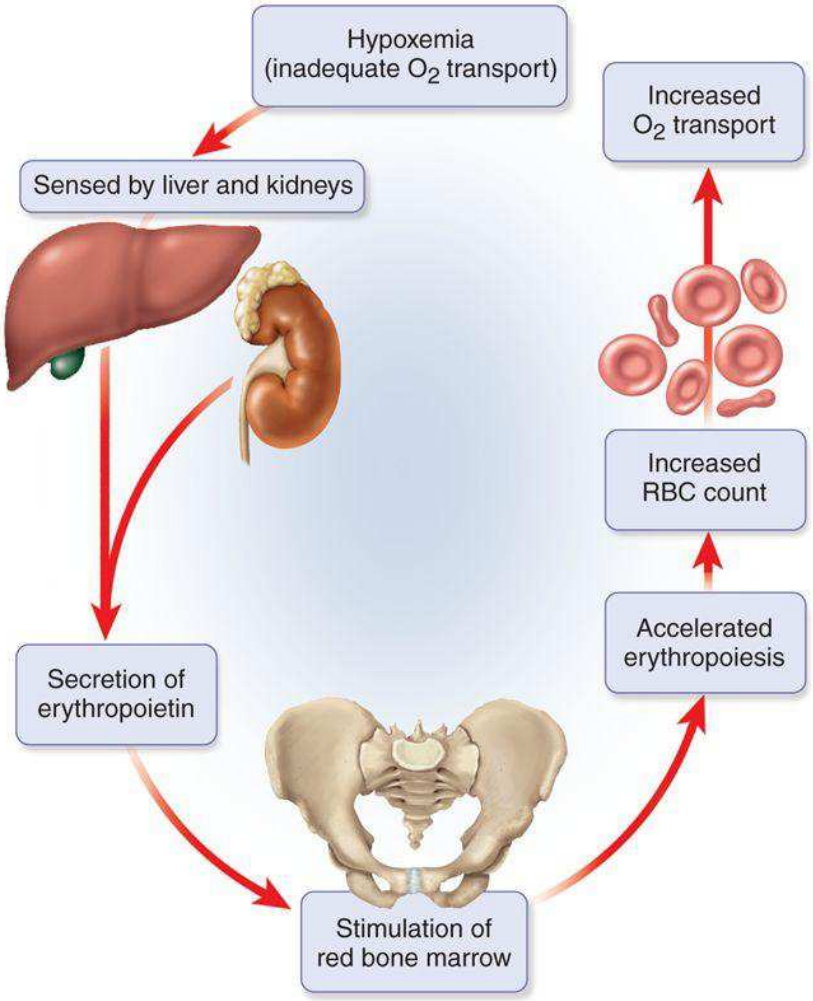
EPO vs. Darbepoetin

SKC In-service Feb 2016

Role of Epo


Hypoxemia (inadequate O_2 transport)
Sensed by liver and kidneys
Secretion of erythropoietin
Stimulation of red bone marrow
Accelerated erythropoiesis
Increased RBC count
Increased O_2 transport

Trade/Generic Names

- Erythropoetin = Epo = Procrit = Epogen = Eprex
- Darbepoetin = Aranesp

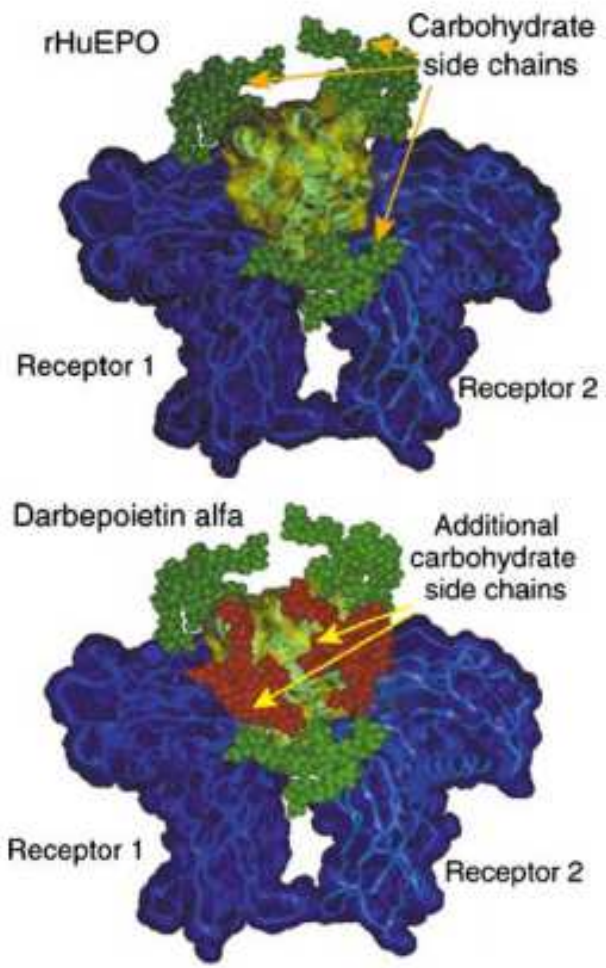


Fig. 4 Molecular comparison of recombinant human erythropoietin (rHuEPO) and darbepoetin alfa, which have the same mechanism of action (from [45], with permission)

Formulations

- Recombinant human erythropoietin (rHuEPO, epoetin alfa)EPO gene cloned 1985; initial clinical trials with epoetin alfa reported in 1986-1989. Approved by US FDA in 1989.
  - Human gene expressed in Chinese Hamster Ovary system. Same amino acid structure and biological activity as native EPO–Contains 3 N-linked carbohydrate chains required for biological activity

- Darbepoetin alfa–Super-sialylated analog of rHuEPO–5 N-linked carbohydrate chains–5 amino acid substitutions to EPO peptide backbone distant from receptor-binding domain–Binds to EPO-receptor with same mechanism of

- “Biosimilars” -soon to come due to Epo going off patent–Retacrit (Hospiria)

Pharmacokinetics / Pharmacodynamics: Epo

- While a much higher peak plasma concentration is achieved after IV bolus administration, it declines at a more rapid rate than after subcutaneous administration (McMahon 1990; Salmonson 1990)
- Onset of action: Several days
- Peak effect: Hemoglobin level: 2 to 6 weeks
- Distribution: V_d: 9 L; rapid in the plasma compartment; concentrated in liver, kidneys, and bone marrow; similar to extracelluar plasma volume in adults (McMahon, 1990; Salmonson, 1990)
- Metabolism: Some degradation does occur
- Bioavailability: SubQ: Premature neonates: 42% (Brown 1993); Adults: 36% (Salmonson 1990); intraperitoneal epoetin alfa: 3% (Macdougall 1989)
- Half-life elimination: SubQ: 16 to 67 hours; IV: 4 to 13 hours
- Time to peak, serum: SubQ: 5 to 24 hours
- Excretion: Feces (majority); urine (small amounts, 10% unchanged in normal volunteers)

Pharmacokinetics / Pharmacodynamics: Darbepoetin

- Onset of action: Increased hemoglobin levels not generally observed until 2 to 6 weeks after initiating treatment
- Distribution: V_d: 0.06 L/kg
- Bioavailability: Adults: ~37%
- Half-life elimination: IV: 21 hours
- SubQ: Dialysis patients: 46 hours (range: 12 to 89 hours)
- **Note:** Darbepoetin alfa half-life is approximately 3-fold longer than epoetin alfa following IV administration
- Time to peak: SubQ: 48 hours (range: 12 to 72 hours; independent of dialysis)

Duration of action

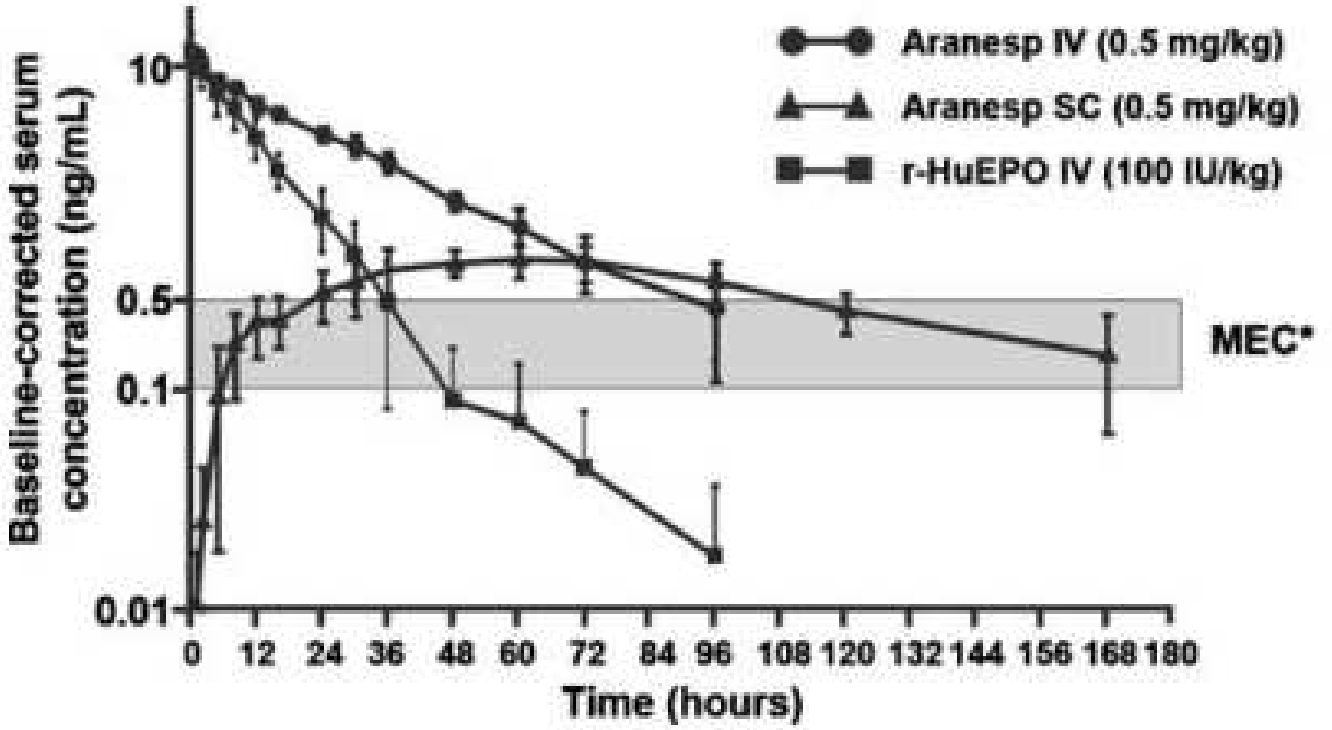
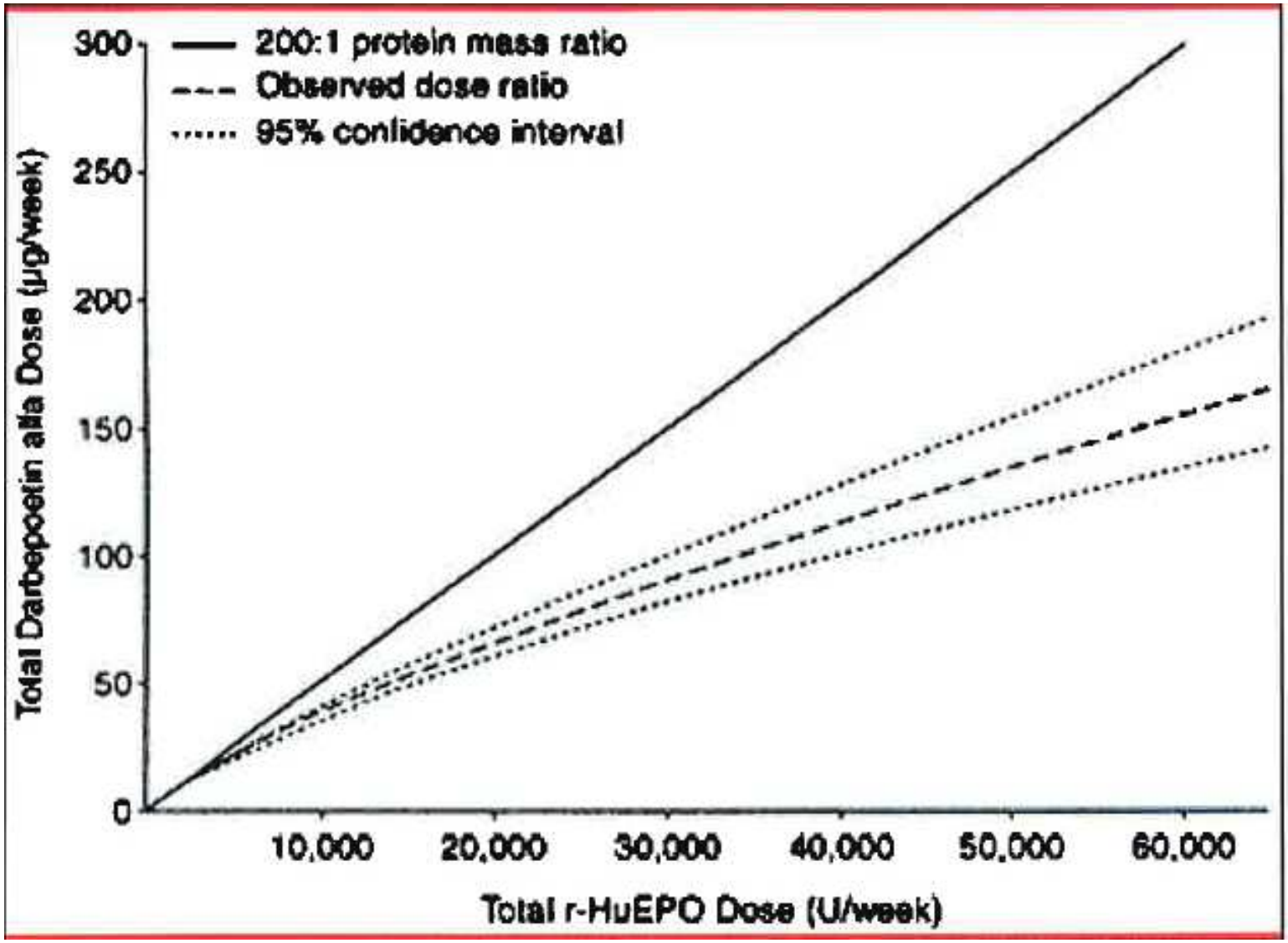


Fig. 5 Darbepoetin alfa serum concentration in stable peritoneal dialysis patients remains above the minimal effective concentration (MEC) for erythropoiesis longer than an equivalent dose of recombinant human erythropoietin (rHuEPO) (from [51], with permission)

Dose Conversion



Dose Conversion*

Previous Weekly Epoetin alfa Dose (Units/week)		Aranesp Dose
< 1,500	1,500	6.25
1,500 to 2,499	2,000	6.25
2,500 to 4,999	3,750	12.5
5,000 to 10,999	8,000	25
11,000 to 17,999	14,500	40
18,000 to 33,999	26,000	60
34,000 to 89,999	62,000	100
≥ 90,000	90,000	200

*Note based on NKC Home dialysis experience manufacturer dose conversion may under-dose patients

NKC Conversion Dosing

Conversion from Erythropoetin to Darbepoetin:

Convert patients currently receiving erythropoietin to darbepoetin as follows:

Current Hgb	Conversion Formula
Less than 10 g/dL	Use a 1:250 (darbepoetin:erythropoietin) ratio (current weekly EPO dose/250) and round up to the nearest darbepoetin dosing step (table 1).
10-11 g/dL	Use a 1:300 (darbepoetin:erythropoietin) ratio (current weekly EPO dose/300) and round up to the nearest darbepoetin dosing step (table 1).
11.1 – 12 g/dL	Use a 1:400 (darbepoetin:erythropoietin) ratio (current weekly EPO dose/400) and round up to the nearest darbepoetin dosing step (table 1).
>12 g/dL	HOLD all ESAs if Hgb greater than 12 and check Hgb weekly
Patients on HOLD from EPO protocol	If EPO on HOLD from the EPO protocol, when Hgb less than or equal to 11.5 g/dL convert erythropoietin to darbepoetin as follows: 1. Calculate 75% of the most recent weekly EPO dose. (Most recent weekly EPO dose before HOLD x 0.75) = new weekly EPO dose. 2. Convert the <u>new</u> weekly EPO to darbepoetin dose using the above conversion formula appropriate for patient's Hgb.

Table 2

Aranesp

- Aranesp single-dose syringes are available in the following strengths:
  - 10 mcg Aranesp/0.4ml
  - 25 mcg Aranesp/0.42 mL
  - 40 mcg Aranesp/0.4 mL
  - 60 mcg Aranesp/0.3 mL
  - 100 mcg Aranesp/0.5 mL
  - 150 mcg Aranesp/0.3 mL
  - 200 mcg Aranesp/0.4 mL
  - 300 mcg Aranesp/0.6 mL
  - 500 mcg Aranesp/1 mL

Administering Aranesp

Procedure	Key Points
1. • **Check patient's order (dose and route).** • **Check the patient record to make sure the patient does not have a latex allergy.**	1. • See NKC Aranesp Standing Orders. Aranesp should be given during the first run of the week. • The needle cover on the pre filled syringes contains latex.
2. Check status of Hgb	• Hgb goal is 10-11 g/dl
3. a. Prefilled Syringes: **Remove the appropriate dose of Aranesp from the refrigerated box. Aranesp should never be frozen and it must be protected from light.** • **Check the expiration date on the syringe label.** • **Do not shake Aranesp.** • **Aranesp can be given anytime during the treatment.**	3. Aranesp pre filled syringes come in color coded boxes of 4 in the following doses: • Gray 10 mcg • Magenta 25mcg • Green 40 mcg • Yellow 60mcg • Red 100mcg

Administering Aranesp

4. Administer Aranesp IV using the port on the Streamline blood tubing's normal saline line. PPE should be worn and good aseptic technique must be utilized.	• **Make sure that the roller clamp on the NS line is closed.** • **Inject the Aranesp.** • **Touch the + and – keys on the dialysis machine to spread the pressure limits** • **Open the clamp and flush the NS line.** • **Observe the pressure limits reset.** **(Limits should reset in about 10 seconds.)**
5. Activate the needle guard by sliding it up over the needle until you hear a click.	• Keep your hands behind the needle itself at all times. • Drop the syringe into a red needle box.
6. Observe the patient for signs of allergic reaction.	• Watch for: a. Itching/ Hives/Rash b. Cough/SOB. c. Rapid heart rate d. Abdominal pain e. Sweating In the event of an allergic reaction, follow the NKC Standing Orders for drug reactions. Complete a progress note in cyberREN and an online QIR as soon as possible. Notify the patient's physician
7. Chart the medication in cyberREN.	

Administering Aranesp

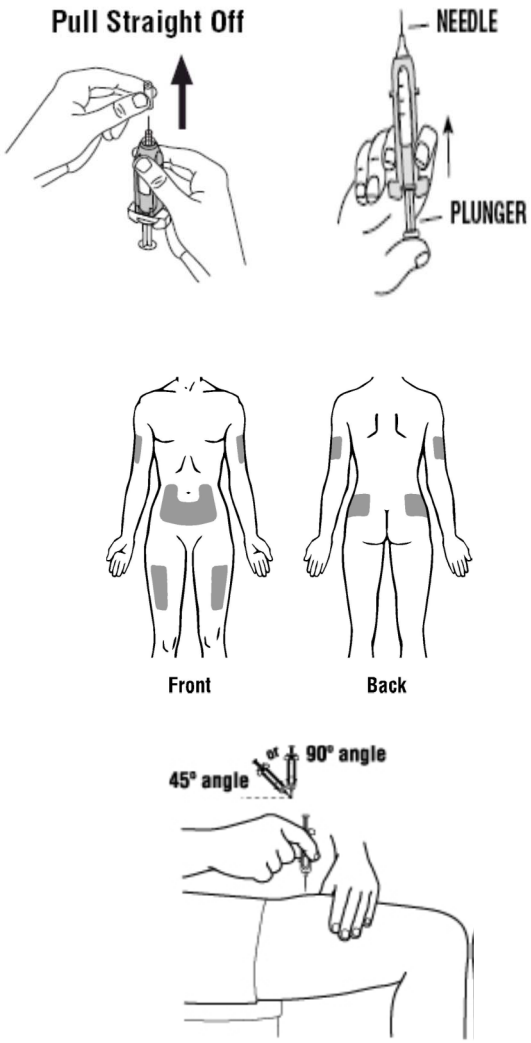
- **Administering Aranesp Do's and Don'ts**:
- Do store Aranesp in a refrigerator between 36-46 degrees F.
- Do keep Aranesp out of the light.
- Do check the expiration date on the syringe or vial.
- Don't use Aranesp is the vial looks cloudy, the liquid has flakes or clumps in it, or it appears foamy.
- Don't shake Aranesp. Shaking can actually deactivate it.
- Don't rely on the color coding. Always check the dose on the vial or pre filled syringe.
- Don't give Aranesp in conjuinction with other medications. No formal drug interaction studies have been done with Aranesp.

Latex Allergy

Administering Aranesp For Patients with Latex Allergy	
1. Complete steps 1 and 2 as above.	
2. Remove the appropriate single dose vial from the refrigerated box. Use the same precautions as above: • Aranesp should not be frozen. • Check the medication expiration date. • Protect the Aranesp from light. • Do not shake Aranesp	2. Most doses of Aranesp are available in single dose vials. The exception is the Gray coded 10 mcg dose. It is only available in the prefilled syringes.
3. Using an NKC approved 1cc med-saver insulin syringe aseptically draw up the required dose.	
4. Complete steps 4-7 above.	

Administering the dose (SQ)

- Clean the site (see below) with an alcohol wipe where the injection is to be made.
- Hold the syringe like you would hold a pencil. Use a quick “dart-like” motion to insert the needle either straight up and down (90-degree angle) or at a slight angle (45 degrees) into the skin. Inject the prescribed dose subcutaneously.
- Pull the needle out of the skin and press gauze over the injection site and hold it there for several seconds. Do not recap the needle.
- Dispose of the used prefilled syringe as described below. Do not reuse the prefilled syringe.



WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

See full prescribing information for complete boxed warning.

Chronic Kidney Disease:

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).**
- **No trial has identified a hemoglobin target level, Aranesp dose, or dosing strategy that does not increase these risks.**
- **Use the lowest Aranesp dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).**

Cancer:

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (Table 3, 5.3).**
- **Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp to patients with cancer (5.2).**
- **Use the lowest dose to avoid RBC transfusions (2.3).**
- **Use ESAs only for anemia from myelosuppressive chemotherapy (1.2).**
- **ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.3).**
- **Discontinue following the completion of a chemotherapy course (2.3).**