

The Safe Use Of Erythropoiesis Stimulating Agents in Oncology Patients

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October 19, 2007

Objectives

- To be aware of the recent safety data concerning thrombotic complications and reduced survival with the use of ESAs in oncology patients
- To review the CCO guidelines and determine how they should be modified in light of the recent data

Disclosures

I have given sponsored talks, attended and chaired advisory boards, been a consultant for and received clinical trials funding, travel expenses and donations to a PMH Foundation education fund in lieu of honoraria from:

- Amgen Canada Inc.*
- Novartis Pharmaceuticals Canada Inc.
- Ortho Biotech, A Division of Janssen-Ortho Inc.*
- Pfizer Canada Inc.
- Roche Canada*
- Schering-Plough Canada Inc.

The Role of Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy Practice Guideline Report #12-1 March 2005

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Guideline Questions

- Does erythropoietin reduce the need for transfusion of red blood cells in patients with non-hematologic malignancies receiving chemotherapy for the treatment of cancer?
- Does erythropoietin improve the quality of life of individuals receiving chemotherapy for the treatment of cancer?

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Target Population

These recommendations apply to cancer patients with non-hematologic malignancies receiving chemotherapy who meet the following criteria:

- Hb levels \leq 100 g/L during the initial courses of chemotherapy,
OR
- Hb levels \leq 120 g/L with symptoms of anemia affecting functional capacity/quality of life,
AND
- Anemia not caused by hemolysis, gastrointestinal bleeding, and iron or folate deficiencies.

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Key Recommendations

Erythropoietin is recommended as a safe and effective treatment option if given with the intent of reducing the incidence of symptomatic treatment-related anemia and the need for red blood cell transfusion

Erythropoietin is recommended as a reasonable treatment option in patients in whom a slow decline in hemoglobin is associated with increased fatigue and perceived reductions in quality of life.

Erythropoietin is not recommended in situations where rapid (i.e. less than 4 weeks) recovery of hemoglobin is required.

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Qualifying Statements

- Transfusion of red blood cells remains the treatment of choice in patients with rapidly developing symptomatic anemia
- It is most reasonable to recommend erythropoietin to individuals who have a reasonable chance of experiencing relatively long-term survival or cure as an outcome from their chemotherapy. It is these individuals who have the greatest risk of suffering from the long-term complications of transfusion. Individuals in whom short survival is anticipated are better treated by transfusion for symptomatic anemia since erythropoietin takes approximately four weeks to start elevating hemoglobin levels.

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Qualifying Statements

- Although the evidence supporting the use of erythropoietin is stronger for patients receiving platinum-based therapy, erythropoietin is also effective in patients receiving myelosuppressive regimens that do not contain platinum
- Several randomized trials have shown statistically significant improvements in several domains of quality of life in patients receiving erythropoietin. The clinical significance of these improvements (often of the order of 20% to 40% increase over baseline) in patients with moderate to severe baseline quality of life impairment (generally 50% of maximum scores) also needs to be considered. A clear linear relationship between fatigue and anemia has not been established.

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Qualifying Statements

- The dose approved in Canada is: 150 IU/kg of epoetin alpha delivered s.c. 3 times a week for 4 weeks, increasing to 300 IU/kg s.c. 3 times a week for 4 weeks if the Hb has not risen by 10 g/L. If, after that time, the endpoints have not been achieved, therapy is discontinued. If the Hb is rising by more than 20 g/L per month, the dose should be reduced by approximately 25%. The target Hb is usually 120 g/L
- It is also reasonable to administer 40,000 IU of erythropoietin once weekly, increasing after four weeks to 60,000 IU once weekly for four weeks, if the endpoints have not been achieved
- There is a rare but clinically significant risk of pure red blood cell aplasia with erythropoietin in patients with chronic renal failure.

Erythropoietin in the Management of Cancer Patients with Non-Hematologic Malignancies Receiving Chemotherapy

Darbepoetin alpha

- The dose schedule is 225 mcg weekly, 675 mcg s.c. every 3 weeks or 500 mcg flat dose every 3 weeks. The target hemoglobin is 120 g/L.

A Summary on Recent Safety Signals Observed (FDA Briefing, March 2007)

- ESAs when administered to target a Hb level of greater than 120 g/L increased the risk of TVEs
- Key pieces of clinical data showing negative survival impact seen in setting where CT not given
 - Head & Neck: \pm surgery followed by RT only
 - NSCLC: palliative RT (\pm non-platinum CT)
 - Anemia of Cancer

<http://www.fda.gov/cder/drug/advisory/RHE2007.htm>

Impact of ESAs on the Frequency of VTE in Oncology Patients

Meta-analysis: Thromboembolic Events

	Control n = 609 No. (%)	Epoetin beta n = 800 No. (%)
Patients with at least one AE	27 (4)	49 (6)
Total number of AEs	29	53

Clinically Relevant TVEs

Tumor type (study)	Patients with TVEs, n/N (%)		Difference, % EPO-control
	Control	Epoetin alfa	
SCLC (EPO-CAN-15)	2/52 (4)	16/52 (31)	27
Gastric, rectal (PR00-03-006)	2/31 (6)	6/28 (21)	15
Cervical (GOG-0191)	5/55 (9)	10/58 (17)	8
SCLC (N93-004)	11/115 (10)	12/109 (11)	1
MBC (EPO-INT-76)	25/456 (5)	36/448 (8)	3
H&N (EPO-GBR-7)	2/149 (1)	4/133 (3)	2
NSCLC (EPO-CAN-20)	2/31 (6)	1/31 (3)	-3
Cervical (AGO/NOGGO)	3/122 (2)	2/119 (2)	0
H&N (RTOG-99-03)	0/68 (0)	1/67 (1)	1

Hemoglobin Restoration Studies Clinically Relevant TVEs

Tumor type (study)	Patients with TVEs, n/N (%)		Difference, % EPO-placebo
	Placebo	Epoetin alfa	
Mixed (cisplatin)	8/65 (12)	6/67 (9)	-3
MM (EPO-INT-2)	1/76 (1)	5/69 (7)	6
CLL (J89-040)	2/79 (3)	9/142 (6)	3
Mixed (EPO-INT-3)	1/65 (2)	8/135 (6)	4
Mixed (EPO-INT-10)	5/124 (4)	14/251 (6)	2
Mixed (PR98-27-008)	6/165 (4)	9/168 (5)	1
Mixed (non-cisplatin)	3/76 (4)	2/81 (2)	-2
Ovarian (EPO-INT-1)	1/80 (1)	3/164 (2)	1
Mixed (non-chemo)	0/59 (0)	1/65 (2)	2
CLL (P-174)	0/12 (0)	0/33 (0)	0

Overall odds ratio (95% CI): 1.55 (0.96, 2.50)

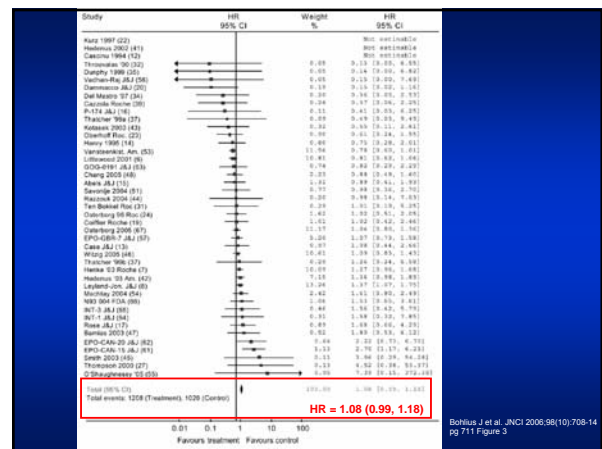
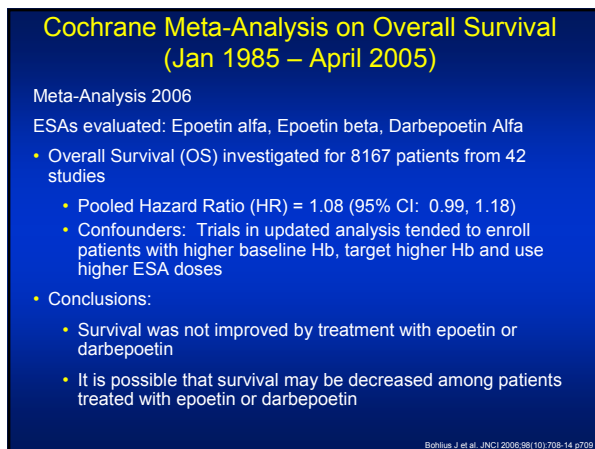
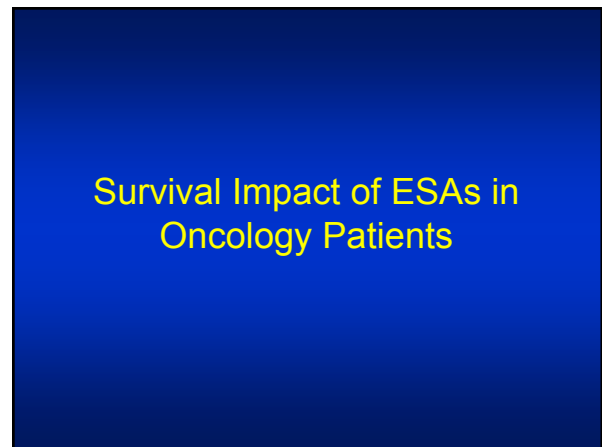
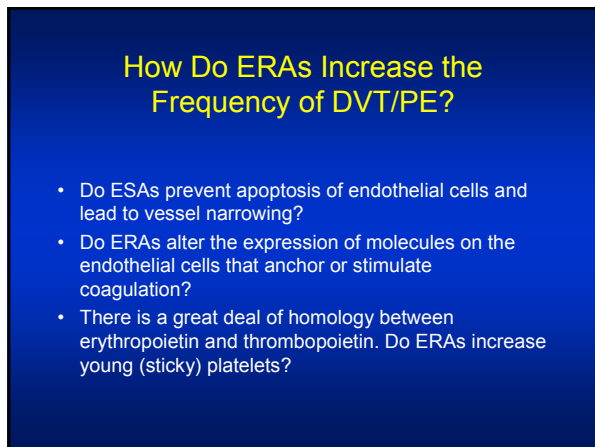
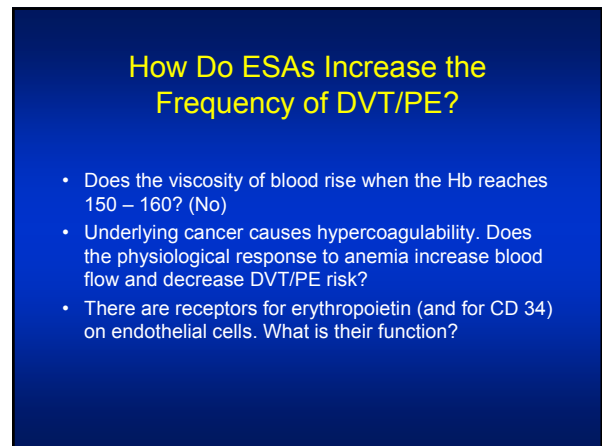
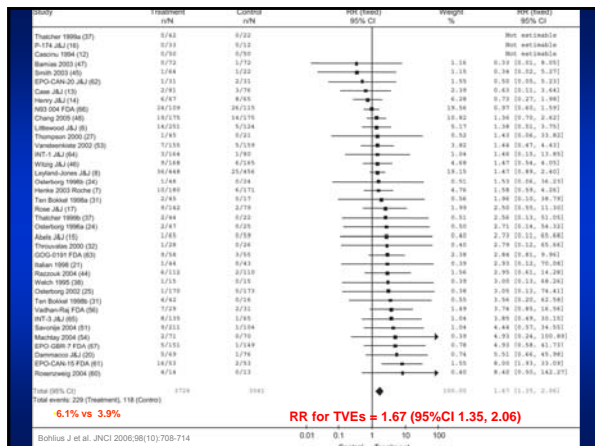
Darbepoetin: Potential Interaction between Prior TE and Treatment

	% of Subjects	
	Darbepoetin (N=1807)	Placebo (N=444)
No Prior Thrombotic Event	6% (97/1703)	3% (11/412)
Prior Thrombotic Event	13% (14/104)	12% (4/32)

Updated Cochrane Meta-Analysis: 1985-2005

- Updated systematic review on efficacy & safety of ESAs
 - 57 trials, 9353 cancer patients
- ESAs evaluated
 - Epoetin alfa, epoetin beta, darbepoetin alfa
- Patients received ESAs for prophylaxis or treatment of anemia in cancer with or without concurrent antineoplastic therapy

Bohlus J et al. JNCI 2006;98(10):708-714
Bohlus J et al., Cochrane Reviews 2006



EPO-INT-76 (Metastatic Breast Cancer)

- Design
 - Epoetin alfa QW or placebo continued for 12 mo regardless of chemotherapy changes or disease progression
 - Initiate at ≤ 130 g/L, target hemoglobin 120 to 140 g/L
 - Primary endpoint 12-mo survival
 - Objective measures of tumor response and disease progression not specified (timing/method)
- Study drug treatment discontinued at recommendation of DSMB, 88% completed or withdrawn

INT-76 Breast Trial: Survival & TTP

12-Month OS

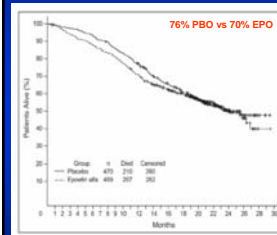


Fig 3. Kaplan-Meier estimate of long-term survival, with convergence of lines about 19 months after randomization (as of January 4, 2003; intent-to-treat (ITT) population, N = 939).

TTP

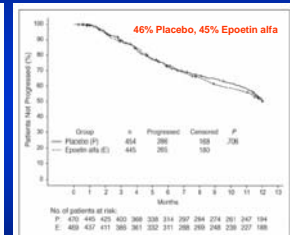


Fig 5. Time to disease progression: intent-to-treat population, N = 939. Forty patients were not assessable.

Leyland-Jones, B et al. JCO 2005;23:5960-72 (p5965 & p5967)

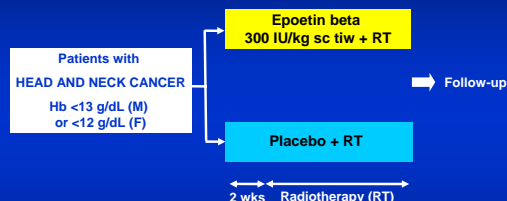
ESAs & Survival Signals in Head and Neck Cancer

Henke (Epo beta)
 RTOG-9903 (Epoetin alfa)
 DAHANCA 10 (Darbepoetin alfa)

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

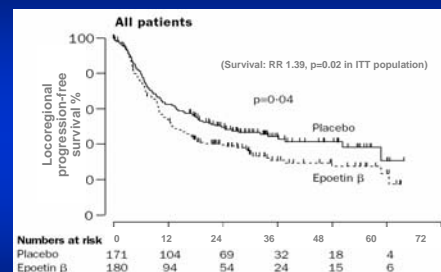
Henke M et al. *Lancet* 2003; 362: 1255-60

MF4449: Study Design



*Patients stratified by TNM (IV vs. III) & tumor resection status:
 Stratum 1: RT after clean margin tumor resection
 Stratum 2: RT after non-radical tumor resection
 Stratum 3: definitive RT alone

ENHANCE Study Locoregional Progression Free-Survival



Henke M et al. *Lancet* 2003;362:1255-60

RTOG-9903 (H&N Cancer) Survival: Design

- Treatment
 - RT alone (66–72 Gy) vs RT + epoetin alfa 40,000 u QW
- Population
 - Non-metastatic, non-resected Squamous cell carcinoma of H&N receiving curative RT
 - N = 372 planned (closed Nov 2003 after 148 enrolled)
- Hb entry / target / dosing
 - Hb 90–135 g/L (up to 125 g/L for women)
 - Withhold dose if Hb >160 g/L for men and >140 g/L for women
 - Dosing: EPO 40K QW (increase to 60K if no Hb increase)
- Endpoints
 - 1^o: Time to Local Regional Failure (LRF)
 - 2^o: LR PFS

Machay M et al. *Int J Radiation Oncology* 2004;60(1) Abstract 5

RTOG-9903 Results

- Study closed to accrual after 148 patients were enrolled
- Interim analysis revealed it would be extremely unlikely that Epo would benefit LRC or OS although preliminary results are not statistically significant
- Results:
 - Hb levels significantly improved in EPO arm
 - No improvement in anti-tumor efficacy
 - No significant difference in the overall rate of Grade 3 toxicity between the two arms

Machay M et al. *Int J Radiation Oncology* 2004;60(1) Abstract 5

RTOG-9903 Results

Treatment	# of pts.	Complete Response rate	1-yr. actuarial LR Control	1-yr. actuarial LR progression-free survival	1-yr. actuarial overall survival
Epo	67	73%	63%	60%	70%
No Epo	68	75%	70%	65%	81%
p-value	---	0.85	0.74	0.65	0.89
Hazard ratio (95% confidence interval)	---	---	1.18 (0.67-2.09)	1.10 (0.65-1.89)	1.57 (0.76-3.27)

- 135 patients evaluable for interim report with median f/u 12 months

Machay M et al. *Int J Radiation Oncology* 2004;60(1) Abstract 5

DAHANCA 10 Squamous Cell H&N Cancer

- Patients with HNSCC treated with primary radiation and Nimorazole
- Hb \geq 14.0 g/dl (9.0 mmol/l) were treated with radiation and not randomized
- Hb < 14.0 g/dl randomized to darbepoetin or placebo
- Five year survival
 - Hb \geq 14.0 g/dl – 70%
 - Hb < 14.0 g/dl – 51%

DAHANCA 10 – Sept 15, 2007 analysis, ECCO 14

DAHANCA 10 Head and Neck Cancer Study



Study endpoints:

- Local-regional control (T+N)
- Overall survival
- Hemoglobin response

Hb entry: \leq 13 g/dL
Withhold dose: Hb >15 g/dL

DAHANCA – Interim Analysis 2007 available at <http://conman.au.dk/dahanca/>

DAHANCA 10 Results

	Darbepoetin	Placebo
5 year LR Control	58%	68%
Overall Survival	39%	51%
VTE	3%	1%

DAHANCA 10: H&N Cancer Study

- Interim Conclusions:
 - Based on outcomes of interim analysis, DAHANCA group concluded that the likelihood that darbepoetin alfa would be better than the control was non-existent
 - Enrollment ended at interim analysis (N=522 enrolled)
 - EPO receptor analysis pending
 - Danish task force is evaluating role of ESAs

DAHANCA – Interim Analysis 2007 available at <http://conman.au.dk/dahanca/>

Anemia of Cancer in Patients NOT Receiving Chemotherapy

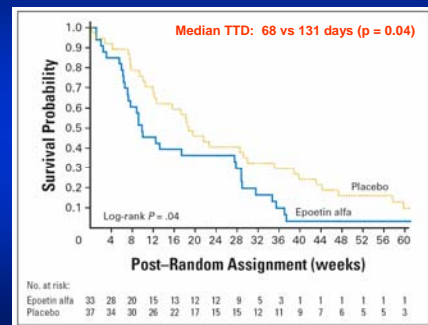
EPO-CAN-20: NSCLC (Epoetin Alfa)
20010103: Anemia of Cancer (Darbepoetin Alfa)

EPO-CAN-20 (Advanced NSCLC)

- Trial terminated November 2003
- Co-operative group collected additional baseline parameters and continued long-term follow-up
- Trial studied advanced Stage III and IV NSCLC patients unsuitable for curative therapy
- Data has been in public domain since 2004
- Data has already been included in the published meta-analyses assessing ERA survival (Bohlus J et al. 2006)

Wright J et al. JCO 2007 Mar 20;25(9):1027-32. Epub 2007 Feb 20

EPO-CAN-20 (Advanced NSCLC)



Wright J et al. JCO 2007 Mar 20;25(9):1027-32. Epub 2007 Feb 20

EPO-CAN-20 (Advanced NSCLC)

Table 3. Reported Causes of Death

Cause of Death	Placebo (34 deaths)		Epoetin Alfa (32 deaths)	
	No. of Patients	%	No. of Patients	%
Progressive lung cancer	31	91.2	28	87.5
Pneumonia	1	2.9	1	3.1
Myocardial infarction	1	2.9	—	—
Renal failure	1	2.9	—	—
Hyponatremia	—	—	1	3.1
Bowel perforation	—	—	1	3.1
Unknown cause	—	—	1	3.1

Wright J et al. JCO 2007 Mar 20;25(9):1027-32. Epub 2007 Feb 20

Darbepoetin Alfa 20010103: Design

- Cancer patients with active cancer no concurrent chemotherapy
- Randomized, Double-blind, placebo-controlled: Darbepoetin alfa 6.75 mcg/kg vs. Placebo, every 4 weeks for 4 doses*
- Multi-center (Western & Central Europe (60%), Eastern Europe, North America, Australia)
- 16 week treatment period with 2 years of follow up to evaluate survival

Goldberg P. The Cancer Letter 33:4, 2007
Amgen.com 2007

Darbepoetin Alfa 20010103: Design

- Primary endpoint: Transfusion rate from week 5 to week 17 (end of study)
- Target Hb 120 g/L and dose held at 130 g/L
- DSMB monitored study at unknown frequency

Goldberg P. The Cancer Letter 33:4, 2007
Amgen.com 2007

Darbepoetin Alfa 20010103: Results

- 989 of 1,000 patients randomized
- N = 985 received study drug (n = 459 darbepoetin alfa, 463 placebo) and 52% completed trial
- Significantly higher number of patients achieved Hb response in the darbepoetin alfa arm

Darbepoetin Alfa 20010103: Results

	Placebo N=470	Darbepoetin Alfa N=515	
Transfusions			
Weeks 5-17	24%	19%	P = 0.064
Mortality			
Weeks 1-17 mortality	20%	26%	
With median mortality (f/u of 4.3 months)	46%	48.5%	HR = 1.29 (95% CI: 1.08 to 1.55), p=0.006

Goldberg P. The Cancer Letter 33:4, 2007; Amgen.com 2007

Hazard Ratio for Overall Survival by Cancer Type

Disease	Number	Hazard Ratio	HR CI
Breast	128	0.90	0.52 – 1.55
Colon	74	0.74	0.38 – 1.45
Kidney	50	1.54	0.71 – 3.34
NSCLC	180	1.24	0.86 – 1.80
Prostate	103	1.51	0.88 – 2.62

Hazard Ratio for Overall Survival by Cancer Type

Disease	Number	Hazard Ratio	HR CI
Stomach	37	1.18	0.50 – 2.79
Ovarian	39	0.80	0.26 – 2.41
Cervix	40	0.80	0.35 – 1.80
NHL	36	2.07	0.59 – 7.25
Myeloma	71	3.38	1.19 – 9.61
Others	227	1.27	0.87 – 1.84

How Do ESAs Increase Tumor Growth?

- Do tumor cells express epo receptors and does epo binding trigger a proliferation pathway?
- Do tumor cells express epo receptors and does epo binding block apoptotic pathways?
- Does an improved Hb level produce better tumor cell oxygenation and diminish hypoxic cell death?
- Does epo stimulate clotting in tumor vasculature and decrease tumor cell oxygenation thereby rendering cells more resistant to radiation and chemotherapy?

Centers for Medicare and Medicaid Services ESA therapy

1. The Hb level immediately prior to initiation or maintenance of ESA treatment is < 10 g/dL
2. The starting dose for ESA treatment is the FDA label starting dose, no more than 150 U/kg/three times weekly for epoetin and 2.25 mcg/kg/weekly for darbepoetin alpha. Equivalent doses may be given over other approved time periods

CMS ESA therapy

3. Maintenance of ESA therapy is the starting dose if the Hb level remains below 10 g/dL 4 weeks after initiation of therapy and the rise in Hb is ≥ 1 g/dL
4. For patients whose Hb rises < 1 g/dl compared to baseline over 4 weeks and whose Hb remains < 10 g/dL after the 4 weeks of treatment, the FDA label starting dose may be increased once by 25%. Continued use of the drug is not reasonable if the Hb rises < 1 g/dl compared to baseline by 8 weeks.

CMS ESA therapy

5. Continued administration is not reasonable if there is a rapid rise in Hb > 1 g/dl over 2 weeks of treatment unless the Hb remains below or subsequently falls to < 10 g/dL. Continuation and reinstitution of ESA therapy must include a dose reduction of 25% from the previous dose.
6. ESA treatment duration for each course of chemotherapy includes the 8 weeks following the final dose of myelosuppressive chemotherapy in a chemotherapy regimen

CMS ESA therapy is not reasonable

1. anemia in cancer or cancer treatment patients due to folate, B-12 or iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
2. anemia associated with the treatment of CML, AML, or erythroid cancers;
3. the anemia of cancer not related to cancer treatment;
4. anemia associated only with radiotherapy;

CMS ESA treatment is not reasonable

5. prophylactic use to prevent chemotherapy-induced anemia;
6. prophylactic use to reduce tumor hypoxia;
7. patients with erythropoietin-type resistance due to neutralizing antibodies; and
8. anemia due to cancer treatment if patients have uncontrolled hypertension.

Ian Quirt's Perspective

- ESA therapy should not be given to patients with head and neck cancer
- We should defer additional studies of ESA therapy in patients receiving radiation therapy
- We should not use ESA therapy for patients with the anemia of cancer
- We should believe in Ontario's guideline process and not emulate the patterns of practice that evolve without data in other countries
- Discovering the mechanisms that produce thrombosis and tumor progression is the key