The Safe Use Of Erythropoiesis Stimulating Agents in Oncology Patients

Ian Quirt
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 ≤ 100 g/L during the initial courses of chemotherapy, OR
- Hb levels ≤ 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

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: surgery followed by RT only
  - NSCLC, palliative RT (non-platinum CT)
  - Anemia of Cancer

Impact of ESAs on the Frequency of VTE in Oncology Patients

**Meta-analysis:** Thromboembolic Events

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Epoetin beta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 609</td>
<td>n = 800</td>
</tr>
<tr>
<td>Patients with at least one AE</td>
<td>27 (4)</td>
<td>49 (6)</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>29</td>
<td>53</td>
</tr>
</tbody>
</table>

**Clinically Relevant TVEs**

<table>
<thead>
<tr>
<th>Tumor type (study)</th>
<th>Patients with TVEs, n/N (%)</th>
<th>Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC (EPO-CAN-15)</td>
<td>2/52 (4)</td>
<td>27</td>
</tr>
<tr>
<td>Gastric, rectal (PR00-03-006)</td>
<td>2/31 (6)</td>
<td>15</td>
</tr>
<tr>
<td>Cervical (GOG-0131)</td>
<td>5/55 (9)</td>
<td>8</td>
</tr>
<tr>
<td>SCLC (893-004)</td>
<td>11/115 (10)</td>
<td>1</td>
</tr>
<tr>
<td>MBC (EPO-INT-76)</td>
<td>25/456 (5)</td>
<td>3</td>
</tr>
<tr>
<td>M&amp;N (EPO-GBR-7)</td>
<td>2/148 (1)</td>
<td>2</td>
</tr>
<tr>
<td>NSCLC (EPO-CAN-20)</td>
<td>2/31 (6)</td>
<td>-3</td>
</tr>
<tr>
<td>Cervical (AGO/NOGGO)</td>
<td>3/122 (2)</td>
<td>0</td>
</tr>
<tr>
<td>M&amp;N (RTOG-99-03)</td>
<td>0/88 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Hemoglobin Restoration Studies Clinically Relevant TVEs**

<table>
<thead>
<tr>
<th>Tumor type (study)</th>
<th>Patients with TVEs, n/N (%)</th>
<th>Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed (Cisplatin)</td>
<td>8/165 (5)</td>
<td>-3</td>
</tr>
<tr>
<td>MM (EPO-INT-23)</td>
<td>1/76 (1)</td>
<td>6</td>
</tr>
<tr>
<td>CLL (389-040)</td>
<td>2/79 (3)</td>
<td>3</td>
</tr>
<tr>
<td>Mixed (EPO-INT-3)</td>
<td>1/65 (2)</td>
<td>4</td>
</tr>
<tr>
<td>Mixed (EPO-INT-10)</td>
<td>5/124 (4)</td>
<td>2</td>
</tr>
<tr>
<td>Mixed (PR98-07-008)</td>
<td>6/165 (4)</td>
<td>1</td>
</tr>
<tr>
<td>Mixed (non-Cisplatin)</td>
<td>37/46 (8)</td>
<td>-2</td>
</tr>
<tr>
<td>Ovarian (EPO-INT-1)</td>
<td>1/81 (1)</td>
<td>1</td>
</tr>
<tr>
<td>Mixed (non-chemo)</td>
<td>0/59 (0)</td>
<td>2</td>
</tr>
<tr>
<td>CLL (P-174)</td>
<td>0/12 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**Darbepoetin: Potential Interaction between Prior TE and Treatment**

<table>
<thead>
<tr>
<th>% of Subjects</th>
<th>Darbepoetin (N=1887)</th>
<th>Placebo (N=444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior Thrombotic Event</td>
<td>6% (97/1703)</td>
<td>3% (11/412)</td>
</tr>
<tr>
<td>Prior Thrombotic Event</td>
<td>13% (14/104)</td>
<td>12% (4/32)</td>
</tr>
</tbody>
</table>

**Updated Cochrane Meta-Analysis: 1985-2005**

- Updated systematic review on efficacy & safety of ESAs
- 57 trials, 9,353 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
RR for TVEs = 1.67 (95% CI 1.35, 2.06)

How Do ESAs Increase the Frequency of DVT/PE?

- Does the viscosity of blood rise when the Hb reaches 150 – 160? (No)
- Underlying cancer causes hypercoagulability. Does the physiological response to anemia increase blood flow and decrease DVT/PE risk?
- There are receptors for erythropoietin (and for CD 34) on endothelial cells. What is their function?

How Do ERAs Increase the Frequency of DVT/PE?

- Do ESAs prevent apoptosis of endothelial cells and lead to vessel narrowing?
- Do ERAs alter the expression of molecules on the endothelial cells that anchor or stimulate coagulation?
- There is a great deal of homology between erythropoietin and thrombopoietin. Do ERAs increase young (sticky) platelets?

Survival Impact of ESAs in Oncology Patients

Meta-Analysis 2006

ESAs evaluated: Epoetin alfa, Epoetin beta, Darbepoetin Alfa

- Overall Survival (OS) investigated for 8167 patients from 42 studies
  - Pooled Hazard Ratio (HR) = 1.08 (95% CI: 0.99, 1.18)
  - Confounders: Trials in updated analysis tended to enroll patients with higher baseline Hb, target higher Hb and use higher ESA doses

Conclusions:
- Survival was not improved by treatment with epoetin or darbepoetin
- It is possible that survival may be decreased among patients treated with epoetin or darbepoetin
**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, 86% completed or withdrawn

**ESAs & Survival Signals in Head and Neck Cancer**

*Henke (Epo beta)*

*RTOG-9903 (Epoetin alfa)*

*DAHANCA 10 (Darbepoetin alfa)*

**MF4449: Study Design**

- Patients with HEAD AND NECK CANCER
  - **Hb <13 g/dL (M) or <12 g/dL (F)**
- **Epoetin beta 300 IU/kg sc tiw + RT**
  - Follow-up
- **Placebo + RT**
  - 2 wks Radiotherapy (RT)

*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

**INT-76 Breast Trial: Survival & TTP**

12-Month OS

TTP

**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*

**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**
  - 1st: Time to Local Regional Failure (LRF)
  - 2nd: LR PFS

**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

**DAHANCA 10 Squamous Cell H&N Cancer**

- Patients with HNSCC treated with primary radiation and Nimorazole
- Hb ≥ 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 ≥ 14.0 g/dL – 70%
  - Hb < 14.0 g/dL – 51%

**DAHANCA 10 Results**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Darbepoetin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year LR Control</td>
<td>58%</td>
<td>68%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>39%</td>
<td>51%</td>
</tr>
<tr>
<td>VTE</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>
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.


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 (Burman J et al. 2006).


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


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.
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

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


<table>
<thead>
<tr>
<th>Transfusions</th>
<th>Placebo (N=470)</th>
<th>Darbepoetin Alfa (N=515)</th>
<th>P = 0.064</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 5-17</td>
<td>24%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-17</td>
<td>20%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>46%</td>
<td>48.5%</td>
<td></td>
</tr>
<tr>
<td>With median mortality (t/u of 4.3 months)</td>
<td>HR = 1.29 (95% CI: 1.08 to 1.55), p=0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio for Overall Survival by Cancer Type

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
<th>Hazard Ratio</th>
<th>HR CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>128</td>
<td>0.90</td>
<td>0.52 – 1.55</td>
</tr>
<tr>
<td>Colon</td>
<td>74</td>
<td>0.74</td>
<td>0.38 – 1.45</td>
</tr>
<tr>
<td>Kidney</td>
<td>50</td>
<td>1.54</td>
<td>0.71 – 3.34</td>
</tr>
<tr>
<td>NSCLC</td>
<td>180</td>
<td>1.24</td>
<td>0.86 – 1.80</td>
</tr>
<tr>
<td>Prostate</td>
<td>103</td>
<td>1.51</td>
<td>0.88 – 2.62</td>
</tr>
</tbody>
</table>

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 ≥ 1g/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