Uses and adverse effects of Erythropoietin

Jonathan Wallis
Consultant Haematologist
Freeman Hospital
Newcastle upon Tyne
UK
Dear Jonathan,

Please would you see this pleasant 45 year old man who is a Jehovah’s witness. His Hb is 12.0g/dl. He has recurrent GI stromal tumour in his abdomen. I plan to remove the tumour surgically. I would be grateful for your advice.

Yours sincerely

Mr Haveago
Effect of Epo in healthy volunteers
### Hip and Knee surgery: Epo day -10 to +5

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>n</th>
<th>%</th>
<th>Mean units transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epo 300 IU/Kg/day</td>
<td>54</td>
<td>17%</td>
<td>0.37</td>
</tr>
<tr>
<td>Epo 100 IU/Kg/day</td>
<td>64</td>
<td>25%</td>
<td>0.58</td>
</tr>
<tr>
<td>Placebo</td>
<td>67</td>
<td>54%</td>
<td>1.42</td>
</tr>
</tbody>
</table>

Epo 300 iu/kg/day x 15 days = Eu 3150
Epo 100 iu/kg/day x 15 days = Eu 1050
One unit red cells = Eu 220
THR at Freeman Hospital: Pre-op Hb versus likelihood of transfusion

% TRANSFUSED PTS VERSUS PRE-OP hb

% patients transfused

PRE OP HB g/L

0.0 100.0 200.0 300.0 400.0 500.0

100 120 140 160 180
1. Only 2-3% of major joint replacement patients in N America receive pre-operative Epo
   Reasons: Cost and inconvenience

2. Targeted pre-op Epo for 2-3 weeks can reduce transfusion requirements and is economically more attractive.
   Average 76000 iu epo ~ Euro 750
Local protocol

Selection of patients:

– Religious objections to transfusion
– Age Younger
– Likely survival Long term
– Likely need for transfusion High (>30%)
Local protocol

- 15 - Hb in g/dl = number of weeks treatment
- Use once weekly epo or darbepoietin
- Monitor weekly
- Give oral iron or iv iron
- Eg: Hb 12g/dl, = 3 weeks Epo = Euro 750
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Mr Haveago
Cancer, Hb and response to DXT

605 women with cervical cancer from 7 centres

Pre-treatment Hb does not correlate with outcome

Hb during DXT correlates with outcome

Anaemic patients transfused prior to DXT did as well as non-anaemic patients

Patients who became anaemic during treatment did as badly as those anaemic and not transfused

Epo in Cancer

Many prospective randomised studies of short term outcome
- Improved Hb
- Reduced transfusion rates
- Improved Quality of life (QoL)

Several retrospective trials looking at long term outcome
- Improved response to treatment and survival compared to historical controls
Erythropoietin in Cancer

Prospective randomised trials


Osterborg et al. BJHaem. 2005; 129: 206-9
Myeloma and NHL
Epo x 16 weeks or placebo
# Erythropoietin in Cancer

Prospective randomised trials with survival as an outcome

1. Osterborg *et al.*  
   Myeloma and NHL  
   *BJ Haem.* 2005; 129: 206-9

2. Littlewood *et al.*  
   Haem & non-haem cancer  
   *J Clin Oncol* 2001; 19: 2865-74

3. Henke *et al.*  
   Head and neck cancer  
   *Lancet* 2003; 362: 1255-60

4. Leyland-Jones  
   Breast cancer  
   *J Clin Oncol* 2005; 23: 5960-72

5. DAHANCA  
   Head and neck cancer  
   Available at [www.DAHANCA.dk](http://www.DAHANCA.dk)

6. GOG-191  
   Cervical cancer  
   *Gynecologic Oncology;* 108: 317-25

7. Prepare study  
   Breast Cancer  
   *FDA notified of results*
stratum 1: Surgical excision + DXT
stratum 2: Incomplete surgical excision + DXT
stratum 3: DXT alone
“Breast cancer trial with erythropoietin terminated unexpectedly”


• Trial closed early
• Poorer outcome in treatment arm
• Possible imbalance in randomisation
# Best trial of Epo in Ca breast


<table>
<thead>
<tr>
<th>Subjects:</th>
<th>939 patients stage 4 disease, first line chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Epo or placebo to keep Hb at 12-14g/dl</td>
</tr>
<tr>
<td>Primary outcome:</td>
<td>Overall survival at 12 months</td>
</tr>
<tr>
<td>Result:</td>
<td>71% vs 76 % in favour of placebo. P = 0.01</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary cause of death</th>
<th>Placebo</th>
<th>Epo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>22% vs 27%</td>
<td></td>
</tr>
<tr>
<td>Chemo toxicity</td>
<td>0.2% vs 1.7%</td>
<td></td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>0.6% vs 1.3%</td>
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</table>
DAHANCA 10 trial

- 484 patients with Head and neck cancer
- Radiation treatment
- Randomised to Epo (darbopoietin) or placebo
- Primary outcome was ‘loco-regional failure’
- Epo arm had 10% higher failure. $p = 0.01$
FDA warning Jan 3rd 2008

GOG-191 study in Ca Cervix
(Thomas et al. Gynecologic Oncology; 108: 317-25)

Prepare study in Breast Ca

‘Both the PREPARE study in breast cancer and the GOG-191 study in cervical cancer showed higher rates of death and or tumor progression in patients who received an ESA compared to patients who did not receive an ESA.’

‘The GOG-191 study stopped enrolling patients because of a higher rate of potentially life-threatening blood clots occurring in the patients who received an ESA.’
Why might Epo be detrimental to survival?

• Epo receptors have been reportedly found in many tissues
• Epo is anti-apoptotic
  – I.e. It reduces cell death
  – Eg. Epo reduces ischaemic brain damage in animals and ? in man
  – Eg. Epo reduces cardiac myocyte death in animals and ? in man
• Some cancers appear to be responsive to Epo in vitro
• Blood vessels feeding cancers may be Epo sensitive
Epo and cancer

Can improve Hb and QoL, and reduce transfusion

Has detrimental effects on some tumours

Breast, Squamous head and neck, Cervical

How do we explain the beneficial effect of high Hb on DXT in Cervical cancer?

?? Due to higher endogenous Epo in anaemic patients having DXT
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Mr Haveago
Does Epo increase likelihood of thrombosis?

Increased incidence of thrombotic events in renal patients on Epo with Hb > 12g/dl

Is thrombosis related to the effect of a higher Hb?

Or to direct effects of Epo?
Epo and thrombosis

ITU study: Corwin et al NEJM 2007, 357; 965
Increased thrombosis in Epo arm despite no benefit to Hb

Numerous trials on presurgical Epo showed no convincing evidence of increased thrombosis

Conclusion
There is an increase in thrombosis with higher HB
There may be a direct effect of Epo on thrombosis.
Appropriate prophylaxis is recommended
ITU study Corwin et al  
NEJM 2007, 357; 965

1460 patients admitted to ITU, 54% trauma  
30,000u Epo weekly for 3 weeks

<table>
<thead>
<tr>
<th></th>
<th>Epo</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>All pts</td>
<td>8.5%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Trauma</td>
<td>3.5%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

**30 day mortality**

HR 0.52 (.27-.99)
Conclusion

1. Epo can reduce peri-operative transfusion requirements
2. Cost and inconvenience remain a barrier to widespread use
3. Should not be used routinely for non-haematological cancer
4. Beware increased risk of thrombosis
5. Cardio/neuro protection may be more interesting than erythropoietic effects, eg see study by Corwin et al
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Dear Jonathan,

Please would you see this pleasant 45 year old man who is a Jehovah’s witness.
His Hb is 12.0g/dl…….

The patient received Epo,
    had a good Hb response,
    survived surgery, lowest Hb =12.8g/dl
    remains alive and well.

Thank you for your attention