Literature Review on the Use of Erythropoiesis-stimulating Agents ESAs in Anaemia in Cancer Patients

The literature and evidence for the use of erythropoietin in treating cancer patients with anaemia has recently been the subject of a review in UpToDate®. The ICON Clinical Team would like to bring to your attention this recent data. The issues around benefits versus potential side effects will be particularly useful when discussing treatment options for anaemia with our patients.

Role of erythropoiesis-stimulating agents in the treatment of anaemia in patients with cancer – UpToDate® Review - Feb 2017
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ICON Summary
This review has been summarised to address the local environment and the agents available in South Africa.

Anaemia in cancer patients may be due to:
- the malignancy itself
- myelosuppressive chemotherapy
- radiation therapy
- or any of the other causes of anaemia that affect patients without cancer.

RBC transfusion is an accepted and reasonable treatment for chemotherapy-related anaemia, particularly if a rapid increase in haemoglobin (Hb) is needed. However, ICON is aware that there is a relative shortage of blood products countrywide and for this and other reasons transfusion is often not the preferred method of rectifying a low Hb in cancer patients on active treatment.

In the patient with cancer and chemotherapy-related anaemia, erythropoiesis-stimulating agents (ESAs) may be used when there is a need to reduce or avoid red blood cell (RBC) transfusions.
For patients with severe symptoms from the anaemia or where rapid rise in Hb is required, transfusion is the recommended option.

Potential side effects of ESAs:
- increased incidence of thromboembolic events
- shortened survival times particularly when used in patients whose anaemia is not due to myelosuppressive chemotherapy. Randomized trials conducted in patients with potentially curable breast, head and neck, and cervical cancer raise the possibility that the use of ESAs might compromise tumor control and survival. In all these trials, the target Hb level was >12 g/dL.
- Use of ESAs may increase the risk of hypertension, thrombocytopenia and/or haemorrhage.

Benefits of ESAs in cancer patients:
- ESAs reduced the use of RBC transfusions. Patients treated with an ESA received one unit less of RBCs on average than control groups in clinical trials.
- There was some suggestive evidence that ESAs improve QOL but this improvement did not reach levels considered to be clinically important relevant. However, most randomized clinical trials have not shown that ESAs prolong survival, or improve quality of life (QOL) or patient-reported outcomes, including fatigue. [2]

Recommendations for the use of ESAs in adult patients with non-haematologic malignancy:
Cancer patients who are being considered for treatment with ESAs should meet all the following criteria:
- Symptomatic anaemia due to chemotherapy for a non-haematologic malignancy.
- ESAs for patients with lower-risk myelodysplastic syndrome to avoid transfusions is an exception to this recommendation.
- An initial Hb level of <10 g/dL should be present (unless patient symptomatic)
- Other treatable causes of anaemia:
  - blood loss
  - haemolysis
  - nutritional deficiency
    - iron
    - B12
    - folate

should be excluded or treated if present.
Iron Deficiency:

Parenteral iron

Parenteral iron augments the Hb response to ESA therapy in some subsets of patients, but not all patients require parenteral iron.

Parenteral iron might be preferred during ESA therapy in patients:

- who have not had an adequate response to oral iron within five to six weeks
- who cannot tolerate or refuse to take oral iron
- with low or low-normal serum iron levels (although it is not yet clear what parameters predict which patients are most likely to benefit from IV, rather than oral, iron.)
- For all patients treated with ESAs, it is recommended that supplemental iron be given to maintain a transferrin saturation ≥20 percent and a serum ferritin ≥100 ng/mL [4,5].

ESMO – The European Society for Medical Oncology (ESMO) considers that for anaemic patients with iron deficiency, IV iron in conjunction with ESAs leads to a higher Hb increment in comparison with either oral or no iron supplementation [3].

Recommendations against the use of ESAs in adult patients with non-haematologic malignancy:

- For patients with anaemia due to a solid tumor or non-myeloid hematologic malignancy who are NOT receiving chemotherapy, it is recommended NOT to use an ESA to treat anaemia. The use of ESAs for patients with lower-risk myelodysplastic syndrome to avoid transfusions is one exception to this recommendation.
- ESAs should be used cautiously in patients with a high risk for thromboembolism, especially in the setting of malignancies that are associated with an elevated risk for thromboembolic complications (eg, multiple myeloma, treated with thalidomide and lenalidomide with either doxorubicin or corticosteroids).

Patient Selection

The determination of the goal of treatment requires clinical judgment in all cases.

- Whether the use of ESAs should be restricted to patients receiving palliative, rather than potentially curative, chemotherapy is controversial. Some FDA-approved labeling states that ESAs are not indicated in patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure [6].
- Updated guidelines for the use of ESAs from ASH/ASCO do not differentiate between patients receiving potentially curative cancer therapy and those undergoing palliative cancer treatment, stating that no study has evaluated outcomes of ESA therapy by subgroups defined by chemotherapy intent [4,5].
If it is the clinician’s opinion that the risks of therapy with an ESA outweigh the benefits of avoiding RBC transfusion then it is recommended that such an opinion is documented.

Risks and Benefits
See table 2. below:

Table 2. Comparison of risks and benefits of erythropoiesis-stimulating agents (ESAs) versus red blood cell (RBC) transfusion for chemotherapy-related anaemia in patients with solid tumors [1]

<table>
<thead>
<tr>
<th></th>
<th>ESAs</th>
<th>RBC transfusion</th>
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<tbody>
<tr>
<td><strong>Risks</strong></td>
<td>Thrombotic events*</td>
<td>Transfusion reactions¶</td>
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<tr>
<td></td>
<td>Potentially decreased survival*</td>
<td>Circulatory overload</td>
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<tr>
<td></td>
<td></td>
<td>Viral infectionΔ</td>
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<tr>
<td></td>
<td></td>
<td>Iron overload</td>
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<tr>
<td></td>
<td></td>
<td>Development of multiple alloantibodies</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>Gradual improvement in haemoglobin/haematocrit</td>
<td>Rapid improvement in haemoglobin/haematocrit</td>
</tr>
<tr>
<td></td>
<td>Gradual clinical improvement</td>
<td>Rapid clinical improvement</td>
</tr>
<tr>
<td></td>
<td>Avoidance of RBC transfusions in some patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Net reduction in transfusion requirements◊</td>
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</table>

* In trials where target haemoglobin was >12 g/dL.
¶ Febrile nonhaemolytic reactions (1:100); hemolytic reactions (1:19,000); transfusion-related acute lung injury (1:1000-1:5000). Δ Hepatitis B, Hepatitis C, HIV.
◊ Average 1 unit per person. ©2017 UpToDate [1]

**Patient counseling regarding the risks and benefits of ESA therapy**
Patients undergoing myelosuppressive chemotherapy for a potentially curative cancer should be counseled as to the risks and benefits of ESA use versus RBC transfusion or chemotherapy dose reduction.
The American Society of Haematology (ASH)/American Society of Clinical Oncology (ASCO) guidelines suggest that the clinician discuss specific issues before prescribing ESAs. See Table 1 below:

**Table 1. Patient counseling regarding the risks and benefits of therapy with an erythropoiesis-stimulating agent for anaemia associated with chemotherapy for malignant disease** [1]

<table>
<thead>
<tr>
<th>The following issues should be discussed with patients regarding the risks and benefits of therapy with an erythropoiesis stimulating agent (ESA) for symptomatic anaemia in patients receiving chemotherapy for malignant disease:</th>
</tr>
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<tbody>
<tr>
<td>1. The goal of ESA therapy for patients with chemotherapy-induced anaemia is to reduce red blood cell (RBC) transfusion requirements.</td>
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<tr>
<td>2. Although there are some suggestions that ESA treatment may improve fatigue or quality of life (QOL) in some patients, the primary goal is to reduce transfusion requirements.</td>
</tr>
<tr>
<td>3. There are potential harms and benefits of ESAs versus RBC transfusions.</td>
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<tr>
<td>4. ESAs have been found to shorten overall survival and/or speed tumor growth in some patients with cancer. It is for this reason that the US Food and Drug Administration (FDA) has indicated that ESAs should not be given to patients who are being treated for cancer when the goal is to cure the patient (of cancer).</td>
</tr>
<tr>
<td>5. ESAs have risks of adverse events, such as blood clots, and individual risk factors for blood clots have to be considered when weighing the risks versus benefits.</td>
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<tr>
<td>6. ESAs are not recommended for patients with cancer who are not receiving chemotherapy or who are receiving radiotherapy without chemotherapy, because ESAs have been associated with an increased risk of death in such patients.</td>
</tr>
<tr>
<td>7. An acknowledgment form needs to be signed by patients to confirm that they have talked to their health care professional about the risks of ESAs.</td>
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</table>


**ESA dose titration and supplemental iron:**

The approved starting dose of epoetin is 150 U/kg three times weekly or 40,000 U weekly, subcutaneously.

The dose should be adjusted in each patient to maintain the lowest Hb level sufficient to avoid red cell transfusions; dose modification guidelines are presented in the table 3 below:

Updated guidelines from ASCO/ASH state that an optimal target Hb concentration cannot be definitively determined based on the available data. Modification to reduce the ESA dose...
is appropriate when the Hb reaches a level sufficient to avoid transfusion, or the increase exceeds 1 g/dL in any two-week period [4,5].

The ASCO/ASH guidelines suggest discontinuing the ESA after eight weeks if the Hb has not increased by more than 1 to 2 g/dL or there is no diminution in the need for RBC transfusion [4,5].

**Table 3. Dosing guidelines for epoetin in adults [1].**

<table>
<thead>
<tr>
<th>Epoetin Alfa</th>
<th>Three times weekly dosing</th>
<th>Weekly dosing</th>
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<tbody>
<tr>
<td>Starting dose (adults):</td>
<td>150 units/kg subcutaneously (SC) three times weekly</td>
<td>40,000 units SC</td>
</tr>
<tr>
<td>Reduce dose by 25 percent if:</td>
<td>Haemoglobin reaches a level needed to avoid transfusion or increases &gt;1 g/dL in any two-week period.</td>
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<tr>
<td>Withhold dose if:</td>
<td>Haemoglobin exceeds a level needed to avoid red blood cell (RBC) transfusion; restart at 25 percent below the previous dose when the haemoglobin approaches a level where transfusions may be required.</td>
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</tr>
<tr>
<td>Increase dose:</td>
<td>To 300 units/kg SC three times weekly, if response is not satisfactory (rise in haemoglobin &lt;1 g/dL after four weeks of therapy and remains below 10 g/dL) to achieve and maintain the lowest haemoglobin level sufficient to avoid the need for RBC transfusion.</td>
<td>To 60,000 units SC weekly, if response is not satisfactory (rise in haemoglobin &lt;1 g/dL after four weeks of therapy and remains below 10 g/dL) to achieve and maintain the lowest haemoglobin level sufficient to avoid the need for RBC transfusion.</td>
</tr>
<tr>
<td>Discontinue if:</td>
<td>After completion of chemotherapy course, or if after eight weeks of therapy there is no response as measured by haemoglobin levels or if transfusions are still required.</td>
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</table>

*Data from: US Food and Drug Administration.*
ICON Summary Recommendations:

- Transfusion is an appropriate treatment for patients whose clinical condition indicates the need for immediate correction of the Haemoglobin (Hb) level, for those in whom reducing the frequency of transfusion is not an important consideration, and in patients who have established general risk factors for thromboembolic events.
- Patients undergoing myelosuppressive chemotherapy for a potentially curative cancer should be counseled as to the risks and benefits of ESA use versus RBC transfusion or chemotherapy dose reduction.
- The use of ESAs rather than transfusion for patients who meet all of the clinical criteria and who do not have a heightened risk for thromboembolic events (e.g., prior history of thromboses, surgery, prolonged periods of immobilization or limited activity, multiple myeloma treated with thalidomide or lenalidomide with doxorubicin or a corticosteroid) is a reasonable treatment option.
- The decision to use an ESA for patients with highly symptomatic anaemia and a Hb level between 10 and 12 g/dL should be determined by clinical judgment, consideration of the risks and benefits of ESAs, and patient preferences.
- Iron supplementation should be considered in all patients who receive ESAs.

Further Data
Meta-analyses of Benefits and Adverse Events.
Multiple meta-analyses have addressed issues of benefit and adverse effects from ESAs [7 - 11].
A year 2012 Cochrane review of 91 trials with 20,102 participants came to the following conclusions [7]:

Benefits:
- ESAs significantly reduced the use of RBC transfusions (relative risk [RR] 0.65, 95% CI 0.62-0.68). Patients treated with an ESA received one unit less of RBCs on average than the control group.
- There was suggestive evidence that ESAs improve QOL (mean change in the 13-item Functional Assessment of Cancer Therapy-Fatigue [FACT-F] scale was 2.08 points [95% CI 1.43-2.72]) on a scale of 0 to 52 points. This improvement was less than the 3.0 increase considered to be a clinically important difference [12].

Adverse Effects:
- The risk of venous thromboembolism (VTE) was increased in patients receiving ESAs (RR 1.52, 95% CI 1.34-1.74). The risk was significantly elevated regardless of the Hb level at baseline (<10, 10 to 12, or >12 g/dL); the impact of target Hb level was not
addressed. Additional information on thromboembolic risk and the relationship between target Hb and VTE risk is addressed in detail below.

- There was strong evidence that ESAs increase mortality during active therapy (on-study mortality, hazard ratio [HR] 1.17, 95% CI 1.06-1.29), and modest evidence that they increase overall mortality (HR 1.05, 95% CI 1.00-1.11). However, when the analysis was restricted to trials of patients receiving chemotherapy, there was only a trend toward higher on-study (odds ratio [OR] 1.10, 95% CI 0.98-1.24) and overall mortality (OR 1.04 95% CI 0.98-1.11), neither of which was statistically significant. In trials of no antineoplastic therapy, use of ESAs significantly increased both on-study mortality (OR 1.34, 95% CI 1.07-1.66) and overall mortality (OR 1.23, 95% CI 1.04-1.45).

- When analysed according to baseline Hb levels, there was a significant increase in overall mortality (OR 1.17, 95% CI 1.06-1.29) and on-study mortality (OR 1.37, 95% CI 1.12-1.68) among patients with baseline levels >12 g/dL but not at lower levels. The impact of target Hb levels was not addressed.

- Use of ESAs significantly increased the risk of hypertension (RR 1.30, 95% CI 1.08-1.56) and thrombocytopenia/haemorrhage (RR 1.21, 95% CI 1.04-1.42).

Summary of 2012 Cochrane Review: [7]

- ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths.
- There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affects tumour control remains uncertain.
- The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences.
- More data are needed for the effect of these drugs on quality of life and tumour progression.
- Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.

References:

2. Bohlius J, Tonia T, Nüesch E, Jüni P, Fey MF, Egger M, Bernhard J. Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in


