Section 2 – Anaemia guidelines

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2.1 Introduction

There is now an expanding choice of erythropoiesis stimulating proteins (ESPs) and a wealth of data on appropriate dosing regimens, approved indications and safety. The cost of ESP therapy is significant and not all patients respond to treatment. Therefore, guidelines addressing the use and the accurate selection of patients most likely to respond to these treatments are vital.

Section 2 covers the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for the use of ESPs in anaemic patients with cancer, originally developed in 2004, and updated in 2006. The strength of these guidelines is that they provide an evidence-based, scientifically sound framework to support the alleviation of symptoms of anaemia through erythropoietin treatment. They may also encourage discussion regarding the value of multidisciplinary approaches to optimising the care of patients with chemotherapy-induced anaemia and fatigue.

Overall Goals

Specific Targets and Aims

The Nurse’s Role

Overall Goals

The overall goals of the guidelines are to restore functional haemoglobin levels, improve the patients’ quality of life (QoL) and to avoid red blood cell (RBC) transfusions.

Specific Targets and Aims

The targets and aims of this module are to:

- Provide evidence-based guidance on the successful management of anaemic patients
- To highlight the recommended target haemoglobin (Hb) concentration of 12–13 g/dL
- To provide information on ESP use – these guidelines are related to adult cancer patients with solid tumours or haematological malignancies
- To increase knowledge and understanding of the use of ESPs to treat anaemia in patients undergoing chemotherapy and/or radiotherapy
- To educate nurses and subsequently patients (nurses need to know what is recommended in the guidelines in order to ensure best practice for their patients)
- To increase awareness and understanding of the possible risks of thromboembolic events and other potential safety issues when using ESPs to treat chemotherapy-induced anaemia
The Nurse’s Role

Nurses are among the best placed professionals to assess patients for risk by reviewing their patients’ history and current health status. Oncology nurses are in a unique position to identify, assess and manage anaemia and fatigue through their frequent contact with patients – allowing them to assess risk and intervene with preventive strategies.

These guidelines will highlight the role that nurses play in identifying and managing anaemia and will highlight some of the risk factors associated with it.

Nursing care protocols for chemotherapy-induced anaemia management may allow more patients to receive chemotherapies on schedule and at full-dose, as well as reducing potential practice variations that could compromise care, promote cost-effectiveness and increase the quality of care for patients. Furthermore, nursing care protocols may enhance the impaired quality of life that has found to be associated with chemotherapy-induced anaemia.1
2.2 What is anaemia?

Anaemia is generally defined as a decrease in red blood cell (RBC) mass, which occurs when the rate of RBC production falls below the rate of RBC destruction, and can be due to RBC destruction, blood loss or impaired RBC production. In terms of laboratory values, this means when RBCs fall below defined thresholds:

- 12–16 g/dL in women
- 14–18 g/dL in men

When this happens, oxygen delivery to the tissues is decreased, tissues become starved for oxygen and patients become weak, lethargic and confused.

Prevalence of anaemia in cancer patients

Grades of anaemia

Anaemia is highly prevalent in patients with cancer. In the US, it is estimated that 1.3 million cancer patients are anaemic. Furthermore, 39% of the 15,000 patients in the recent European Cancer Anaemia Survey (ECAS) population were classified as anaemic, although the rate did vary depending on the tumour type, disease status, and cancer treatment status.

In both cases, the number of patients receiving treatment for anaemia was very low: 20% in the US study, and 40% in the ECAS study.

Chemotherapy has been shown to be associated with the development of anaemia. In the ECAS study, those patients who received chemotherapy (either alone or in combination with radiotherapy) had the highest incidence of anaemia (63% and 42%, respectively). While a study by the Pacific Shores Medical group showed that 65% of those who were not anaemic at baseline became anaemic during the first 12 weeks of chemotherapy.

Grades of anaemia

The severity of anaemia may be graded according to haemoglobin (Hb) concentration (according to the World Health Organization):

<table>
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<tr>
<td>Grade 0 – normal</td>
<td>Hb within normal limits (14–18 g/dL for men and 12–16 g/dL for women)</td>
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<tr>
<td>Grade 1 – mild</td>
<td>Hb 9.5–10.9 g/dL</td>
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<tr>
<td>Grade 2 – moderate</td>
<td>Hb 8.0–9.4 g/dL</td>
</tr>
<tr>
<td>Grade 3 – serious/severe</td>
<td>Hb &lt;6.5–7.9 g/dL</td>
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2.3 How is chemotherapy associated with anaemia?

The aetiology of anaemia associated with cancer is multifactorial. Treatment-induced anaemia occurs as a result of bone marrow damage (infiltration); haemolysis; renal, hepatic or endocrine disorders or nutritional deficiencies. In addition, radiotherapy and most cytotoxic chemotherapeutic agents can also cause some degree of myelosuppression, and blood loss following radical cancer surgery can also trigger anaemia.1

Non-treatment-induced anaemia in patients with cancer occurs as a result of the tumour and is referred to as anaemia of cancer.
2.4 What are the implications of anaemia for the patient?

Impact on chemotherapy treatment outcome

Quality of life issues

Impact on chemotherapy treatment outcome

The relationship between anaemia and treatment outcome remains poorly characterised in cancer patients.

Quality of life issues

Many of the consequences of anaemia (e.g. cardiovascular, gastrointestinal and vascular symptoms) can adversely affect the quality of life (QoL) of patients and possibly alter their response to cancer treatment. Please refer to Appendix 1 for information on QoL measurement scales.

Despite a new-found understanding of the impact of chemotherapy-induced anaemia on QoL, (through fatigue, depression, nausea and the inability of patients to work or fulfil their social roles), studies show that 50–60% of anaemia remains untreated. This has led to the management of anaemia becoming an integral part of quality treatment for cancer patients.
2.5 How is anaemia recognised?

Anaemia is a frequent finding in cancer patients and should be carefully assessed. Understanding which patients are at risk, and the importance of the symptoms make it possible to manage this important condition.

Associated risk factors

Anaemia-related symptoms

Associated risk factors

Key factors involved in the pathogenesis of cancer-related anaemia include the disease itself, haemodilution, bleeding, hyperplenism, haemophagocytosis, renal insufficiency, haemolysis, nutritional deficiency, bone marrow damage, and treatment, including chemotherapy, radiotherapy and surgery.6

Other co-factors that may also influence the clinical symptoms include:6

- The patient – age and comorbidity
- The malignancy – whether it is uncontrolled and whether there is underlying organ impairment
- The therapy – whether there is overall cardio- or pulmonary toxicity, or underlying infection or bleeding

Anaemia-related symptoms

Typical symptoms can include:10

- Fatigue, defined as a persistent, subjective sense of tiredness that interferes with usual functioning.11
- Headache
- Breathlessness
- Dizziness
- Palpitations and tachycardia
- Impact on work and social life, such as decreased work tolerance, social isolation and reduced sexual activity
- Impact on mental health, including fear, lethargy, concentration deficits, and depression

It is worth noting that patients with chemotherapy-induced anaemia can be asymptomatic.
2.6 How is anaemia managed?

Before erythropoiesis stimulating proteins (ESPs) were introduced into anaemia treatment in the 1980s, allogeneic red blood cell (RBC) transfusions were the only treatment available. Transfusions are still used in severe cases but they do not provide long-term correction of anaemia. Cloning of the human EPO gene in 1983 provided the way forward for the treatment of chemotherapy-induced anaemia.

Additional causes of anaemia such as iron deficiency, bleeding, nutritional defects or haemolysis should be corrected prior to ESP therapy.

Blood transfusions – advantages and disadvantages

Erythropoiesis stimulating proteins

Iron supplementation – in combination with erythropoiesis stimulating proteins

Blood transfusions provide an immediate response and are still indicated in the treatment of acute, severe anaemia (e.g. Hb levels <7–8 g/dL). Though the effects of a transfusion are immediate, the response is not sustainable and transfused RBCs are often functionally defective with a shorter survival time. In addition, approximately 20% of blood transfusions are associated with adverse reactions, some of which may be severe and/or life threatening.

Obviously, the outcome of these blood transfusions would have an effect on the length of stay in hospital and further treatment required by the patients. There are a number of concerns about the use of blood transfusions, all of which have an impact on hospital care, including:

- Introduction of a serious infection such as hepatitis C and HIV
- Iron overload
- Immunosuppression
- Haemolysis
- Limited supply of blood
- Risk of giving incorrectly matched blood

Erythropoiesis stimulating proteins

Erythropoietin is the hormone produced in the kidneys responsible for controlling red blood cell production (erythropoiesis). Recombinant forms of the hormone produced by recombinant DNA technology, such as recombinant human erythropoietin (rHuEPO), are able to provide a more sustained correction of anaemia and offer an improved risk/benefit profile compared with transfusions. In addition, the ability to synchronise certain ESP treatments with regular outpatient visits may be more convenient for patients and healthcare professionals.
The efficacy of ESPs in chemotherapy-induced anaemia has been confirmed both in terms of increasing Hb levels, decreasing RBC transfusion requirements and improving quality of life (QoL).²

The recommendations of the task force concerning the use of ESPs in anaemia patients with cancer are summarised in Figure 1 below.²

Figure 1. Suggested dosing algorithm for erythropoietic proteins in patients with anaemia due to cancer or its treatment.²*

N.B. Target haemoglobin (Hb) levels are not above 13g/dL.

* This figure reflects recommendations from the EORTC anaemia guidelines, and it should be noted that, currently, ESPs are only approved for the treatment of chemotherapy-induced anaemia. Healthcare professionals should refer to the appropriate summary of product characteristics (SmPC) before prescribing ESPs. It should be noted that ESPs are currently only approved for the treatment of chemotherapy-induced anaemia.

Iron supplementation – in combination with erythropoiesis stimulating proteins

Recent studies provided evidence that supplementation with intravenous (IV) iron can improved response to unspecified rHuEPO.¹⁵,¹⁶ In other studies, patients who initially did not respond to treatment with rHuEPO showed improved response when given IV iron.¹⁷,¹⁸ The dosing and schedules for IV iron supplementation are no yet well defined.² Studies currently ongoing in this area should provide answers to this and other questions in this rapidly changing area.²

Currently, the evidence for oral iron supplementation is conflicting and is therefore not recommended for use in combination with ESPs.²
2.7 Who is recommended for treatment with erythropoiesis stimulating proteins?

According to the EORTC guidelines, treatment with erythropoiesis stimulating proteins (ESPs) should be initiated in cancer patients* with a haemoglobin (Hb) level of 9–11 g/dL receiving chemotherapy and/or radiotherapy and those with chemotherapy-induced anaemia, based on anaemia-related symptoms.2

ESPs may be considered in asymptomatic anaemic patients with an Hb level of ≤11.9 g/dL to prevent a further decline in Hb according to individual factors (e.g. type/intensity of chemotherapy, baseline Hb) and the duration and type of further planned treatment.2 Prophylactic use of ESPs to prevent anaemia in patients undergoing chemotherapy and/or radiotherapy who have normal Hb values at the start of treatment is not recommended.2

In addition, ESPs should be initiated in addition to red blood cell (RBC) transfusion for anaemic patients who are transfusion-dependent.2

Age should not determine who receives ESPs, as elderly patients experience the same benefits from treatment with ESPs as younger patients.2

It should also be noted that ESPs are not recommended in patients undergoing autologous blood stem cell transplants, and for patients undergoing allogeneic blood stem cell transplants, ESPs can only be recommended on an individual basis.2

* Currently, ESPs are only approved for the treatment of chemotherapy-induced anaemia. Healthcare professionals should refer to the appropriate summary of product characteristics (SmPC) before prescribing ESPs. It should be noted that ESPs are currently only approved for the treatment of chemotherapy-induced anaemia.
2.8 What are the goals of erythropoiesis stimulating protein therapy?

Treatment should be initiated with the goal of increasing haemoglobin (Hb) concentration to 12–13 g/dL.\textsuperscript{2}

The goal of erythropoiesis stimulating protein (ESP) therapy should be to improve quality of life (QoL) and prevent transfusions.\textsuperscript{2} It is not recommended that ESPs should be used with the aim of improving survival or response to treatment.\textsuperscript{1}
2.9 Which erythropoiesis stimulating protein should be used?

There are currently three erythropoiesis stimulating proteins (ESPs) approved in Europe for the treatment of chemotherapy-induced anaemia:

1. Epoetin alfa (Eprex®)
2. Epoetin beta (NeoRecormon®)
3. Darbepoetin alfa (Aranesp®)

N.B. Please refer to the detailed prescribing information for each product for a full description of indications and dosing.

All three ESPs have demonstrated clinical efficacy in the treatment of chemotherapy-induced anaemia. Any decision on which ESP to use, or how to dose, should take into account efficacy data, as well as convenience for the patient and the healthcare team.

For more specific information on the dosing of ESPs, please refer to Appendix 2. For full prescribing information please refer to the Summary of Product Characteristics.

When should treatment with erythropoiesis stimulating proteins be initiated?

What other patient factors should be considered before treating with erythropoiesis stimulating proteins?

Side effects of erythropoiesis stimulating proteins

When should treatment with erythropoiesis stimulating proteins be initiated?

Treatment for chemotherapy-induced anaemia with ESPs should be initiated at a haemoglobin (Hb) level of 9.0–11.0 g/dL based on anaemia-related symptoms, according to the EORTC guidelines.

As yet, there is no evidence to support the use of ESPs to prevent anaemia, although ESPs may be considered in asymptomatic, anaemic patients with an Hb level of ≤11.9 g/dL to prevent a further decline in Hb, according to individual factors and the duration and type of further planned treatment.
What other patient factors should be considered before treating with erythropoiesis stimulating proteins?

Additional causes of anaemia should be treated/corrected prior to treatment with ESPs, for example:

- Iron deficiency
- Nutritional deficiency (e.g. lack of vitamin B₁₂, folic acid)
- Bleeding
- Hereditary factors
- Renal dysfunction
- Haemolysis

Side effects of erythropoiesis stimulating proteins

1. Pure red cell aplasia (PRCA) – has not been reported following treatment with ESPs in patients with chemotherapy-induced anaemia.²

   The EORTC guidelines recommend that the fear of PRCA should not lead to ESPs being withheld in patients with cancer.²

2. Hypertension – there is a slightly elevated risk (1.25-fold) of hypertension in anaemic cancer patients receiving ESPs.³

3. Thromboembolic events – there is evidence that the risk of thromboembolic events is slightly elevated (1.6-fold compared with controls) in anaemic cancer patients receiving ESPs; however, this may be related to the target Hb level achieved.³

Further data are required to address the risk factors for thrombosis following treatment with ESPs. However, the Hb level should be targeted between 11–12 g/dL to decrease the risk of thrombotic complications.¹²
2.10 Why predict the response to erythropoiesis stimulating proteins?

The guidelines recognise that there are currently no predictive factors of response to erythropoiesis stimulating proteins (ESPs) that can be routinely used in clinical practice. Factors that may affect the response to ESPs include functional iron deficiency, inflammation, infection, surgery, bleeding, haemolysis and folate or vitamin B$_12$ deficiency. In order to increase cost-effectiveness and provide optimal benefit to patients, it would be beneficial to predict a patient’s response to ESPs and identify non-responders as early as possible. As such, there is an obvious need for easy-to-use algorithms for predicting the response.

**Erythropoietin level**

**Potential predictors of response**

**EORTC recommendations**

**Erythropoietin level**

A low serum erythropoietin (EPO) level is the only predictive factor to have been explored, but data has only shown its potential in haematological patients. To date, a dose-response relationship for ESPs has not been clearly observed; although there is indirect evidence to suggest an 8–18% increase in responders after an increase in dose. Higher initial doses of ESPs, however, are not recommended.

**Potential predictors of response**

Strategies already used in the hunt for indicators of response include baseline parameters, such as serum erythropoietin levels, transferrin saturation, baseline haemoglobin (Hb) concentration/transfusion need, platelet count, functional iron deficiency and degree of anaemia. In addition, initial 2- or 4-week increments in factors such as Hb concentration, reticulocyte count and serum transferrin receptor may also be useful predictive factors.

In pooled data from four randomised studies, baseline erythropoietin levels < 100 mU/mL and baseline ferritin < 400ng/mL appeared to have the highest sensitivities as predictive factors and were statistically related to Hb response, although no single factor showed much improvement in sensitivity compared with the overall response rate of 68%. Change in Hb at 4 weeks was the single most important predictor of response ($p<0.0001$).

**EORTC Recommendations**

If functional iron deficiency or vitamin deficiency is ruled out, a low serum EPO level (in particular in haematological malignancies) is the only verified predictive factor of some importance. Values must be interpreted relative to the degree of anaemia present.
Appendix 1. Quality of life assessment measures.

Quality of life (QoL) is a developing science and considered to be an important decision-making tool. It is vital that regulatory bodies recognise the value in QoL assessments and understand that patients are the best judges of quality of life effects.

QoL should be considered in terms of the burden to both patients and healthcare professionals. Using the currently available quality of life measures, the QoL data obtained may help in the clinical decision-making process for these patients. These include more general tools, such as:

- WHO Performance Status Indicator
- Linear Analogue Scale Assessment (LASA)

There are also more cancer-specific scales, which come from the Functional Assessment of Chronic Illness Therapy (FACIT) quality of life measure:

- Functional Assessment of Cancer Therapy-Anaemia (FACT-An)
- FACT-fatigue (FACT-F)

N.B. Please refer to the Abbreviation section for a full list of abbreviations used.

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Appendix 2. EORTC recommendations for the dosing of erythropoiesis stimulating proteins (ESPs).2*

- Within reasonable limits of body weight, fixed doses of ESPs should be used
- The decision to dose-escalate is not generally recommended in patients not responding within 4–8 weeks
- Treatment should be continued until the ≤12–13 g/dL Hb level is reached and patients show symptomatic improvement. For patients reaching the target Hb, individualised treatment with increased intervals of dosing and/or titration of lowest effective maintenance dose should be made repeatedly
- The QW application of epoetin alfa (40,000 IU) is common practice (Grade B) and registered in many countries
- The QW application of epoetin beta (30,000 IU) is registered for haematological diseases and its use in solid tumours is based on data provided for licensing extension (Grade B)†
- The use of darbepoetin alfa (2.25 µg/kg) given QW or Q3W has been shown to be effective in randomised trials (Grade A) and is registered
- There is Grade C evidence to support the use of darbepoetin alfa in Q2W or Q4W dosing intervals
- The evidence for using higher than standard initial doses is very limited, therefore, higher initial doses of ESPs cannot be recommended with epoetin alfa, epoetin beta, or darbepoetin alfa

* This information on the dosing of ESPs reflects recommendations from the EORTC anaemia guidelines, and it should be noted that, in some cases, it may differ from currently approved product labelling.

Healthcare professionals should refer to the appropriate summary of product characteristics (SmPC) before prescribing ESPs. It should be noted that ESPs are currently only approved for the treatment of chemotherapy-induced anaemia.

† Please note that, since the publication of the EORTC anaemia guidelines, epoetin beta has received approval for its use in patients with solid tumours.

N.B. Please refer to the Abbreviation section for a full list of abbreviations used.
### Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ECAS</td>
<td>European Cancer Anaemia Survey</td>
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<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
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<tr>
<td>EPO</td>
<td>erythropoietin</td>
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<td>ESPs</td>
<td>erythropoiesis stimulating proteins</td>
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<tr>
<td>FACIT</td>
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<tr>
<td>FACT-F</td>
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<td>international units</td>
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<td>Linear Analogue Scale Assessment</td>
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<td>PRCA</td>
<td>pure red cell aplasia</td>
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<tr>
<td>RBC</td>
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<tr>
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