

# Haematology

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## Safe and efficacious use of recombinant human erythropoietin in malignancy

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Recombinant human erythropoietic proteins (rhEpo) can be used in anaemic patients with malignancy receiving chemotherapy to reduce transfusion requirements and improve quality of life. It is highly efficacious when used with appropriate intravenous (iv) iron supplementation to combat functional iron deficiency. There is no indication that rhEpo improves either survival or the outcome of treatment; its safety remains under scrutiny since recent studies have indicated increased mortality in patients on rhEpo, although some of them have significant methodological flaws. Recent meta-analyses suggest that, while thromboembolic risk is increased, overall morbidity and mortality is not affected. Drug acquisition costs of rhEpo are high, but need to be balanced against the true costs of blood transfusion.<sup>1</sup> RhEpo is not currently available in the UK NHS pending an appeal with the National Institute for Health and Clinical Excellence.

This article addresses the current status of rhEpo and offers guidelines to ensure its safe use and to achieve high response rates.

### Treatment of the anaemia of malignancy

Most patients treated for malignancy will experience anaemia due to blood loss, nutritional deficiency and bone marrow infiltration. Chemotherapy and radiotherapy-induced suppression of erythropoiesis double the numbers of patients with anaemia.<sup>2</sup> Cytokine dysregulation in malignancy leads to functional iron deficiency in which iron stores are rendered inaccessible to erythropoiesis.<sup>3</sup> Anaemia leads to impaired quality of life, is often under treated and is one of many factors contributing to the morbidity of malignancy, particularly fatigue (the most commonly reported symptom).<sup>4</sup> Transfusion has been the standard of

care, but the experience of using rhEpo in anaemia of chronic renal failure (CRF), where the mechanisms of cytokine dysregulation through chronic inflammation may be similar, has led to its successful application in malignancy.

Although anaemia is a risk factor for poor outcome and treatment-refractoriness in malignancy, particularly haematological<sup>3</sup> and in patients receiving radiotherapy,<sup>5</sup> there is at present no evidence that improving haemoglobin levels has an impact on treatment outcome or survival. Anaemia may merely be a marker of more aggressive, advanced or treatment-refractory disease.

### Recombinant human erythropoietic proteins

Erythropoietin (Epo) is a hormone secreted by the interstitial cells of the renal cortex whose role is central to erythropoiesis. It operates through dimeric transmembrane receptors in cell membranes predominantly of red cell precursors, but is also found in other tissues where its role is not clear. Binding of Epo leads to conformational change, triggering autophosphorylation of a tyrosine kinase (JAK-2) anchored to the intracellular portion of the receptor.<sup>6</sup> A cascade of phosphorylations leads to transcription of the genes responsible for stimulating and sustaining

### Key Points

**Most patients with malignancy are anaemic due to treatment and tumour-related factors**

**Anaemia of malignancy is under-treated and the standard of care is usually transfusion**

**Recombinant human erythropoietic protein (rhEpo) therapy can improve quality of life and reduce transfusion requirements in these patients**

**Intravenous (iv) iron supplementation can overcome the functional iron deficiency common in malignancy and improve rhEpo responsiveness**

**RhEpo increases risk of venous thromboembolism and may increase morbidity and mortality if haemoglobin targets are too high (12 g/dl is the recommended target)**

**Up to 90% of patients with malignancy may respond to rhEpo with appropriate iv iron supplement guided by iron deficiency parameters**

**KEY WORDS:** anaemia, erythropoietin, functional iron deficiency, iron supplementation, malignancy, recombinant human erythropoietin

erythropoiesis. Epo production is predominantly stimulated by detection of hypoxia, including that induced by anaemia. This leads to increased levels of a small polypeptide, hypoxia-inducible factor (HIF) – usually degraded by physiological levels of oxygen – which is a transcription factor promoting Epo gene expression.<sup>7</sup>

### Recombinant human erythropoietic proteins for malignancy

#### Efficacy

RhEpo has been used successfully in the anaemia of renal failure for almost 20 years following successful isolation and cloning of the responsible gene.<sup>8</sup> Much of the experience of efficacy and safety of both rhEpo and adjuvant iv iron is therefore drawn from the renal literature. A decade of use of rhEpo in malignancy has shown improved quality of life and reduced risk of transfusion,<sup>9,10</sup> but meta-analyses have shown no impact on survival or outcome.<sup>11</sup>

The duration, durability and proportion of patients responding to rhEpo are increased by iv iron supplementation.<sup>12,13</sup> Response rates are increased to 80–90%,<sup>14</sup> enabling decreased dosing or early discontinuation of rhEpo. The challenge of rhEpo stimulation will often render a patient iron deplete, blunting their haemoglobin response. Oral iron is ineffective, probably due to the malabsorption associated with inflammation.<sup>12,13</sup> Guided iv iron supplementation appears to be the safest and most cost-effective method of optimising rhEpo response, although ascertainment of functional iron deficiency remains problematic with many of the biochemical parameters themselves altered by disseminated malignancy and chemotherapy.

Identifying rhEpo-responsive patients prospectively has proved difficult. Scoring systems based on iron parameters, serum Epo levels and early haemoglobin and reticulocyte count responses are not usefully predictive in clinical practice.<sup>15</sup>

Weekly epoetin alpha/beta or fortnightly darbepoetin is of similar efficacy

to thrice weekly epoetins, with cost-effectiveness, tolerability and patient convenience guiding their use.<sup>16</sup>

#### Safety

Hypertensive reactions are observed in patients receiving rhEpo, but can usually be managed conservatively and rarely warrant discontinuation of treatment. Initial concerns that rhEpo may precipitate pure red cell aplasia were allayed when it was found to be associated only with certain formulations of epoetin alpha.<sup>17</sup>

Concerns remain regarding the safety of rhEpo, particularly thromboembolic risk and stimulation of malignant cells through Epo receptors which have been found on a wide range of malignant cells, both haematological and non-haematological.<sup>18</sup> *In vitro* testing has demonstrated upregulation of intracellular anti-apoptotic and proliferative factors, but little evidence suggesting promotion of malignant cell growth *in vitro* or in xenografted tumours.<sup>19,20</sup>

There is growing evidence that thromboembolic risk<sup>21</sup> and adverse cardiovascular events are increased at normal and supranormal haemoglobin levels induced by rhEpo therapy.<sup>22</sup> Some clinical trials in malignancy continue to suggest a trend towards poorer outcome, including mortality, tumour progression and thromboembolic risk, among patients receiving rhEpo.<sup>23</sup> These studies had in common high target haemoglobin levels, some of them included patients not receiving chemotherapy, and at least two had severe methodological flaws – with the groups receiving Epo tending to have more advanced, aggressive disease. As a result of these studies, the US Food and Drug Administration (FDA) has insisted upon a ‘black-box warning’ about the potential for tumour promotion and thromboembolic events, and requires rhEpo to be withheld from patients whose haemoglobin level exceeds 12 g/dl until the level falls below 11 g/dl.

Clearly, caution should be exercised in using rhEpo and more conservative haemoglobin targets set. Further trials are necessary, especially in the use of rhEpo in patients not receiving chemotherapy.

A recent meta-analysis found that thromboembolic risk is doubled with rhEpo, but did not demonstrate increased mortality or morbidity overall.<sup>11</sup>

Administration of iv iron is widespread in CRF. Many of the initial concerns about its safety, including increasing infection risk, potentiation of malignant cell growth, tissue damage through oxidative stress, and iron overload, have not been demonstrated clinically.<sup>24</sup> Newer iron formulations (low molecular weight dextrans and sucrose salts) have considerably reduced potential for anaphylaxis and intolerance.

### Guidance for use of recombinant human erythropoietic proteins

The guidelines discussed below are based on the European Organisation for the Research and Treatment of Cancer<sup>25</sup> and American Society of Haematology/American Society of Clinical Oncology<sup>26</sup> guidelines, with modifications following the iv iron supplementation data and safety concerns with higher haemoglobin targets. Although data suggest benefit of rhEpo in patients not receiving chemotherapy, current guidelines recommend that it should be restricted to those receiving chemotherapy.

#### Starting therapy

Commencement of rhEpo should be guided symptomatically and only following investigation and correction of reversible causes of anaemia such as nutritional deficiency and active bleeding. Studies have suggested that starting rhEpo with higher haemoglobin levels may be of benefit, but a more cautious approach based on symptoms may be more appropriate. Our practical approach is to have a haemoglobin threshold below 10 g/dl before considering rhEpo treatment.<sup>14,25,26</sup> Symptomatic response to haemoglobin increase has been found to be greatest at 11–12 g/dl, with diminishing benefit and considerable risk at higher values. A rise in haemoglobin of at least 2 g/dl is considered clinically significant.

## Dose

Initial dosing of rhEpo should be 40,000 units weekly with epoetin alpha, 30,000 units weekly with epoetin beta or 300 µg fortnightly (or 500 µg every three weeks) with darbepoetin.

## Iron status markers

Iron status markers should be measured at baseline, including serum ferritin, transferrin saturation and zinc protoporphyrin if available. Additional factors of value include reticulocyte haemoglobin content (CHR) and mean corpuscular haemoglobin (MCH). Iron status should be checked during rhEpo therapy at weeks 4, 8 and thereafter as indicated by a suboptimal haemoglobin response. If two or more iron-deplete values are present at baseline (particularly transferrin saturation or zinc protoporphyrin) in the face of an adequate serum ferritin, iv iron should be started. This represents functional iron deficiency. A trend towards iron depletion during rhEpo therapy (particularly a falling serum ferritin), even while the absolute values remain in the normal range, should also trigger iv iron supplementation.<sup>27</sup> This may take the form of weekly (200 mg) iron sucrose injections or 'total dose infusion' (ie 1 g for practical purposes) with low molecular weight iron dextran at the physician's discretion.

## Failure to respond

If a haemoglobin increment of less than 1 g/dl is achieved in four weeks (even with iron supplementation, if necessary), the patient should be considered refractory to rhEpo. Dose escalation could be considered (to 60,000 units weekly for a further four weeks) or the therapy terminated and a transfusion programme instituted. Target haemoglobin levels should be guided by symptomatic response, but safety concerns at higher haemoglobin levels indicate that correction to the normal range may be hazardous. Current recommendations from the FDA are for a target haemoglobin of 12 g/dl.

## Conclusions

RhEpo use in malignancy is efficacious but uptake is limited by expense and concerns about its safety. Further high quality trials are necessary, but the bulk of evidence demonstrates a positive impact on quality of life and transfusion requirements in patients receiving chemotherapy without having an impact on survival. Haemoglobin targets should be conservative and based on symptomatic response, with iv iron supplementation to ensure maximal response in patients deemed functionally iron deficient. Using this approach, response rates of 80–90% are being achieved in anaemic cancer patients receiving chemotherapy.<sup>12,13,14,27</sup>

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## Lymphoma

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### diagnosis: an update

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Malignant lymphomas are a heterogeneous group of tumours that arise from cells of the immune system. Over 40 distinct clinicopathological entities are currently recognised under the broad heading of lymphoma, a number that is bound to increase as understanding of disease biology advances. The clinical picture, treatment and prognosis of these disorders may be very different so diagnostic accuracy is of paramount importance. Genetic and phenotypic markers can also predict prognosis and response to treatment within individual disease categories – of increasing relevance given the availability of risk-adjusted and targeted therapies.

This article summarises the current approach to lymphoma diagnosis and indicates how it is likely to evolve in the future.

### Lymphoma classification

Advances in basic cellular and molecular biology, combined with the application of new investigative techniques, have transformed our understanding of the lymphomas over the last 25 years. Descriptive classifications based on morphological appearance have given way to the current World Health Organization (WHO) system (Table 1),<sup>1</sup> which integrates information on the cellular origin of the tumour with its genetic and phenotypic features and the clinical picture. This works well for B cell lymphomas,<sup>2</sup> but is at present less satisfactory for the T cell disorders as the normal counterpart of the malignant cell is often unknown.

### Clinical presentation

The complexity and ubiquitous nature of the immune system mean that lymphomas can present to almost any specialty with symptoms and signs that depend on the underlying disease biology and the anatomical site(s) involved. Some lymphomas pursue a highly indolent course with few symptoms or signs for many months or years; others progress rapidly, sometimes following an initial low-grade phase. Nodal enlargement is a common presentation but a significant number occur at extranodal sites such as the skin, gastrointestinal tract, lung, thyroid and parotid glands, frequently in association with chronic infection or organ specific autoimmunity.<sup>3</sup>

### Diagnosis

The result of a blood count and film should always be available before performing invasive investigations since this may be all that is required to identify conditions such as chronic lymphocytic leukaemia (CLL) and non-malignant disorders like glandular fever. A number of viral infections are associated with lymphoma, including HIV, human T lymphotropic virus-1 and hepatitis C, whilst others such as hepatitis B can reactivate during chemotherapy. Screening for these viruses is therefore recommended.

As a general rule, lymph node enlargement present for six weeks without explanation should be considered suspicious of lymphoma and the patient referred appropriately, although sometimes abnormalities such as large-volume mediastinal lymphadenopathy will demand immediate action. Wherever possible, excision biopsy of the involved lymph node remains the preferred route to diagnosis because it gives information about tissue architecture and ensures the availability of adequate material for more detailed analysis. For some investigations, fresh tissue is preferable to traditional formalin fixation. Robust protocols must be in place to ensure prompt processing.

Lymphadenopathy involving the head and neck should be investigated in conjunction with an ear, nose and throat or faciomaxillary specialist since squamous