Recombinant human erythropoietin in cancer-treatment related anaemia.

A submission to the NICE technology appraisal process on behalf of the Royal College of Physicians, Royal College of Radiologists, the Association of Cancer Physicians and the Joint Collegiate Council for Oncology

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The National Institute for Clinical Excellence (NICE) is currently appraising the clinical and cost effectiveness of recombinant human erythropoietin (rHuEPO, including epoetin alfa & beta and darbepoetin alfa) versus standard care, in the treatment of cancer-treatment induced anaemia. This document will not form a detailed evaluation of the published literature but rather a clinical interpretation of the data from the viewpoint of a practising Oncologists.

1 Introduction

The development of anaemia is frequent in cancer patients. The anaemia may either be a consequence of the disease process or treatment given to treat that cancer. Anaemia is routinely defined by the level of haemoglobin (Hb) in peripheral blood. The normal level of Hb for males (13 to 18 g/dL) is a little higher than the normal for women (12-16 g/dL). The majority of the published literature makes no distinction between these different normal ranges, defining anaemia as a Hb less than 12 g/dL. Two major documents which guide the clinician in the use of erythropoietin in cancer-treatment related anaemia, the Clinical Practice Guidelines of the American Society of Clinical Oncology and the American Society of Hematology (Rizzo et al, 2002) and more recently the Cochrane Review (Bohlius et al, 2004) both recognise two categories of anaemia; those with a Hb less than 10.0 g/dL and those with a Hb less than 12.0 g/dL (less severe anaemia).

It is important to stress that for many clinicians, anaemia is a more subjective entity that reflects many factors beyond the serum Hb concentration. The patient’s ability to tolerate a level of Hb is often dictated by co-existing morbidity such as cardiovascular or respiratory disease. In general, young patients are able to tolerate a lower Hb than more elderly patients.
1.1 Cause Of Anaemia In cancer patients

The anaemia associated with cancer may be multi-factorial, many causes of which do not reflect a deficiency of erythropoietin. The anaemia may be caused by a combination of blood loss, haemolysis and impaired red blood cell production (erythropoiesis). Impaired erythropoiesis in turn may be caused by nutritional deficiencies (iron, folate, vitamin B12) or bone marrow infiltration. It is essential to carefully assess each patient to treat such problems before commencing erythropoietin. This should include a detailed history and physical examination, a full blood count including blood film, and additional tests to exclude vitamin B12 deficiency (> 148 pmol/L), folate deficiency (> 4.5 nmol/L) and iron deficiency (transferrin saturation < 15% and serum ferritin < 10 ng/mL). These alternative causes of anaemia must be excluded and if present treated, in any patient in whom recombinant erythropoietin is being considered.

It has more recently been appreciated that many patients with cancer-related anaemia have impaired erythropoiesis due to either an absolute or functional deficiency of erythropoietin. In these patients, serum erythropoietin levels may be inappropriately low for the degree of anaemia (Miller et al, 1990), or the response to circulating erythropoietin may be blunted. It is likely that it is these patients which may benefit from the administration of recombinant erythropoietin. An impaired response to erythropoietin may also occur in the presence of cytokines, which may be elevated in many patients with cancer and often used in the management of malignancies such as renal cancer and melanoma.

1.2 Symptoms of anaemia

Anaemia in cancer patients may be associated with many symptoms which may impair their quality of life (QoL) These include fatigue, dizziness, shortness of breath on exertion, palpitations, headache and depression. Anaemia may also impair a patient’s ability to perform everyday tasks.

It is often the general fatigue, reduced exercise capacity and reduced sense of general well-being which is the most important impact of cancer related anaemia but the hardest to define. A recent study from Sweden assessing the effect of erythropoietin on exercise capacity, physical functioning and general well-being (Lindholm et al, 2004) demonstrated a clear relationship between serum Hb and exercise capacity and a more variable, but statistically significant relationship between serum Hb and self-reported scores of physical functioning and self-reported general health.
1.3 Incidence of anaemia in cancer patients

1.3.1 Anaemia at diagnosis

Many cancer patients are anaemic at diagnosis before any treatment commences. The prevalence of anaemia in cancer patients prior to treatment has been reviewed by Knight and colleagues (Knight et al, 2004). Although the variable levels of Hb used to define anaemia complicate review such as this (ranging from 9.5 to 13.0 g/dL), between 30 and 90% of patients with cancer were anaemic at diagnosis.

1.3.2 Treatment induced anaemia

The frequency of anaemia and its relationship to cancer treatment has been defined in two large-scale studies.

A UK study audited the frequency of anaemia and the use of blood transfusions in 2719 UK patients with ovarian, lung, breast and testicular cancer (Barrett-Lee et al, 2000). They demonstrated that, prior to commencing chemotherapy, anaemia was present in approximately 20% of all patients. However after 6 cycles of chemotherapy significant differences in rates of anaemia were identified. The rate of anaemia in ovarian cancer patients had increased to ~ 50%, in lung to ~ 49%, in testicular ~ 54% and in breast ~ 18%.

The European Cancer Anaemia Survey (ECAS) assessed more than 15,000 patients and identified an overall prevalence (i.e. frequency at enrolment) of anaemia of 39.3% (Ludwig et al, 2004). Most patients (29.3%) had mild anaemia (Hb between 10.0 and 11.9 g/dL); moderate anaemia was recorded in 8.7% (Hb between 8.0 and 9.9 g/dL) and severe anaemia in 1.3% (Hb < 8.0 g/dL). Additional findings include:

- Hb was demonstrated to correlate significantly with WHO performance status (PS) with a mean PS of 1.7 in patients with severe anaemia, 1.4 in moderate anaemia, 1.0 in mild anaemia and 0.8 in patients with Hb > 12.0 g/dL.

- Frequency of anaemia was related to cancer treatment: 39.7% of patients receiving no treatment were anaemic at least once during the survey compared to 75.0% of patients receiving chemotherapy, 38.2% of patients receiving radiotherapy and 61.9% of patients receiving concomitant chemo-radiotherapy.

- The incidence of anaemia in patients not anaemic at enrolment was 53.7% (38.5% mild, 13.8% moderate, 1.4% severe). Anaemia was most frequent in patients receiving chemotherapy (62.7%) compared to radiotherapy (19.7%) or concomitant
chboroietin for cancer treatment related anaemia (41.9%). The incidence was also most frequent in patients with lung cancer (70.9%) and gynaecological cancer (64.6%).

2 Management of anaemia

Four options currently exist for the management of anaemia in cancer patients. These include no treatment, supplementation with iron, blood transfusion and erythropoietin.

The majority of patients who become anaemic in routine clinical practice currently do not receive any intervention. Data from ECAS confirms this with 61.1% of anaemic patients receiving no treatment.

In patients who do receive treatment, this is often not commenced until patients become moderately or severely anaemic (mean Hb of 9.7 g/dL within ECAS). The use of iron, oral or parenteral, is not uncommon (6.5% within ECAS). However, little data supports its use. Within the UK, blood transfusion probably forms the mainstay of treatment.

2.1 Blood transfusion

Blood transfusion is a fast and effective way of correcting the Hb level. However, several limitations do exist for this approach, for example, transfused blood has a shorter half-life than blood generated from a patient's own bone marrow and therefore the effect of blood transfusion is often not long-lasting. Blood transfusion is also not without risk and includes the risk of transmission of viral infection such as HIV and hepatitis, transfusion reaction due to blood incompatibility, and problems associated with fluid overload.

A significant disadvantage associated with blood transfusion is the need for the blood to be administered at hospital, either in outpatients or not infrequently as an inpatient. The Barrett-Lee study identified 25% of patients who required inpatient admission to receive a blood transfusion with a mean length of stay of 1.5 days. This need for a hospital bed or 'chair-time' in out-patients often competes with patients receiving chemotherapy and is often a cause of delays and cancellations to that treatment.

It is vital in any assessment of cost effectiveness that the use of alternatives such as erythropoietin is compared to the total cost of blood transfusion. In addition to the cost of the blood and its preparation, this must include the hospital time/admission associated with its administration, and the nursing and doctor time required to arrange a blood transfusion. Transport costs should also be considered.

Blood is also a finite resource and with recent restrictions on blood donors, very real concerns have been expressed regarding blood supply. The use of an effective alternative
such as recombinant erythropoietin offers a very real alternative to blood transfusion in cancer patients, an option not available in the management of patients undergoing surgery or with trauma.

2.2 Recombinant erythropoietin

Human erythropoietin is a 166 amino acid, 34 kD glycoprotein hormone. It is the principal regulator of red cell production stimulating the proliferation and differentiation of erythroid precursors in the bone marrow. Recombinant erythropoietin (Epoetin alfa, Eprex®, Ortho-Biotech®) and Epoetin beta (NeoRecormon®, Roche®) is a 165 amino acid protein with an almost identical sequence to the native protein. Darbepoetin alfa (Aranesp®, Amgen®) is a modified protein with amino acid substitutions that introduce additional glycosylation sites and give a molecule of three-fold longer half-life.

2.2.1 Epoetin alfa (Eprex®, Ortho-Biotech®)

Eprex® is licensed for

The treatment of anaemia (Hb < 10.5 g/dL) and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy).

Eprex® is given as subcutaneous injection either as 150 IU/kg 3 times/week or a single 40,000 IU dose weekly.

Eprex is most frequently given in cancer patients on the weekly schedule. However, with the majority of chemotherapy administered on a 21 day schedule, the administration of Eprex® requires support of a district nurse or the patient to be educated in administering their own injection.

2.2.2 Epoetin beta (NeoRecormon®, Roche)

NeoRecormon® is licensed for

Prevention and treatment of anaemia in adult patients with solid tumours and treated with platinum-based chemotherapy prone to induce anaemia (cisplatin: 75mg/m²/cycle, carboplatin: 350mg/m²/cycle). Treatment of anaemia in adult patients with multiple myeloma, low grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, who have a relative erythropoietin deficiency (low serum erythropoietin level in relation to the degree of anaemia) and are receiving anti-tumour therapy.
NeoRecormon® is given as subcutaneous injection at a dose of 450 IU/kg per week. This total weekly dose may be divided into three or seven injections. Both schedules require home administration of NeoRecormon®, either with the support of a district nurse or with the patient educated to administer their own injection. Roche have developed the Reco-Pen® to facilitate self-administration by patients.

2.2.3 Darbepoetin alfa (Aranesp®, Amgen).

Aranesp® is licensed for

The treatment of anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Aranesp® is administered subcutaneously at a recommended initial dose of 6.75 µg/kg. The extended half-life of Aranesp® allows the drug to be administered once every 3 weeks. Weekly schedules of 2.25 µg/kg are also possible. A fixed dose of darbepoetin (325 µg once every 3 weeks) has also been assessed and demonstrated to be broadly equivalent in efficacy to a weight based dose (Hesketh et al, 2004).

A three weekly schedule works well in patients receiving chemotherapy, which is often given on a 21-day cycle. Aranesp® may therefore be administered by chemotherapy nurses in outpatients whilst the patient is receiving chemotherapy negating the need for administration by the district nurse or the patient.

2.2.4 General comments

Advice for all three agents suggest dose escalation in patients who fail to respond (Hb increase < 1 g/dL) after 4 weeks or patients who require blood transfusion during the first 4 weeks of therapy. Caution is also advised to restrict the rate of increase in haemoglobin to less than 2 g/dL per month and to discontinue treatment if haemoglobin levels exceed 14 g/dL. It is also recommended to continue treatment for a month following the end of chemotherapy.

Little evidence is available to allow a direct comparison of efficacy of these three agents. A randomised controlled trial has compared darbepoetin alfa (dose escalated from 0.5 to 8.0 µg/kg weekly) to epoetin alfa 150 IU/kg 3 times per week and in a second phase darbepoetin alfa (at four doses from 3 to 9 µg/kg weekly) to epoetin alfa 150 IU/kg 3 times per week (Glaspy et al, 2002). However, this study was designed principally as a dose-finding study for darbepoetin and therefore a comparison of efficacy is not possible.
Both Eprex® and NeoRecormon® require a subcutaneous injection three times per week. A 33% dose escalation allows Eprex® to be administered weekly. The majority of chemotherapy schedules are based on a 21 day cycle and therefore Aranesp® is likely to be more convenient for the patient and the clinical team in arranging its administration.

2.2.5 Concomitant iron therapy

Many patients fail to respond to erythropoietin and all three agents advise dose escalation. However, evidence is accumulating regarding the need for concomitant parenteral iron therapy. A recent phase III trial has assessed the effect of concomitant iron therapy on the frequency and quality of haematological response to erythropoietin therapy (Auerbach et al, 2004). In patients with chemotherapy related anaemia (defined as Hb < 10.5 g/dL, serum ferritin ≤ 450 pmol/L or ≤ 675 pmol/L with transferrin saturation ≤ 19%), IV iron dextran given in addition to epoetin alfa (Eprex®) increased the frequency and magnitude of Hb response and improved QoL compared to epoetin alfa alone. Haematological response (≥ 2 g/dL) was seen in 68% of patients receiving IV iron compared to 25% receiving no iron and 36% receiving oral iron. Mean Hb responses were significantly higher with concomitant iron compared to no iron (2.5 g/dL versus 0.9 g/dL). The study also demonstrated improvements in energy, activity and overall QoL with the addition of IV iron.

This is an important study, which influences the interpretation of the literature that precedes it. If it is possible to increase the efficacy of erythropoietin from 25% to 68% with concomitant iron, it is likely that the magnitude of the benefit possible with erythropoietin are likely to be increased. **It is important that this information is born in mind when considering the results of the Cochrane Review.**

The Auerbach study has also assessed the benefits of oral iron. This demonstrated no significant benefit over control (no iron). A convenient and effective schedule of IV iron was described (iron dextran 100mg IV bolus at each visit). In view of the recognised allergic reactions to iron dextran, a slow infusion of 25 mg was administered for the first three cycles prior to the remainder of the dose.

3 Clinical efficacy of erythropoietin

The clinical efficacy of erythropoietin has been comprehensively reviewed by the Cochrane collaboration (Bohlius et al, 2004). This study assessed all randomised control trials up to and including March 2001. After exclusion of inadequate/inappropriate studies the Cochrane Review evaluated 27 studies with a total of 3287 participants. The Cochrane Review does
not include the studies that reported after this date and in particular has not assessed the efficacy of darbepoetin.

3.1 Haematological Response

The success or failure of erythropoietin therapy was defined as the proportion of participants who had an increase of Hb level $\geq 2$g/dL. By this definition, haematological response was observed in 48% of 1338 participants in the erythropoietin group (range 9% to 70%) compared to 11% of the 1009 participants (range 0% to 27%) in the control group. This corresponds to a relative risk for haematological response with erythropoietin of 3.6 (95% CI 3.07 to 4.23, 14 trials, n=2347). The benefit was seen in patients with both solid and haematological malignancies and in patients receiving platinum or non-platinum based therapy.

In 6 studies (755 participants) the change in Hb achieved was reported. The mean Hb change ranged from $-0.8$ g/dL to $+3.9$ g/dL in patients treated with erythropoietin and from $-3.05$ g/dL to $+0.6$ g/dL in the control group.

25 trials (3069 patients) reported the percentage of participants receiving blood transfusions. The relative risk to receive red blood cell transfusion was significantly reduced by 33% for participates treated with erythropoietin (relative risk 0.67; 95% CI 0.62 to 0.73).

13 studies (2056 participants) recorded the number of red blood cell units transfused per participant. Erythropoietin treatment reduced the units of blood received by each patient by an average of 1.00. This data demonstrated a statistically significant benefit for patients receiving erythropoietin with on average, the erythropoietin group receiving 1 unit of blood less than the control group.

The Cochrane Review concludes that, in patients with malignant disease and an Hb level < 10 g/dL:

- rHuEPO achieves haematological response independent of transfusion.
- rHuEPO reduces the relative risk to receive red blood cell transfusions, but the effect size might be influenced by the underlying disease.
- rHuEPO modestly but statistically significantly reduces the number of red blood cell units transfused per patient.
The efficacy of darbepoetin was not assessed within the Cochrane Review. A number of studies have been published which demonstrate its clinical efficacy (Glaspy et al, 2002; Vansteenkiste et al, 2002; Kotasek et al, 2003).

3.1.1 Comment

In clinical practice the effect of rHuEPO will be judged by its ability to effectively treat cancer-treatment related anaemia. The Cochrane review appears to suggest that rHuEPO's ability to prevent blood transfusion and reduce the number of units transfused is limited with up to 10 patients requiring treatment to prevent one patient receiving a blood transfusion. This conclusion is drawn as (appropriately) the data for both responders and non-responders is combined. However, for patients in whom rHuEPO is effective, the clinical benefit is more significant. Two key issues therefore arise

1) How to improve the response rate with rHuEPO.

As previously discussed, parenteral iron may be effective at achieving this as will the appropriate dose escalation.

2) How to identify non-responders.

Pre-treatment serum erythropoietin has been proposed as a mechanism to predict response to rHuEPO (Cazzola et al, 1995) but other studies have not confirmed this (Glimelius et al, 1998; Oberhoff et al, 1998). After two weeks of therapy patients who have a serum erythropoietin level $> 100$ mU/mL and a Hb rise of $< 0.5$ g/dL are unlikely to respond, whereas patients with a serum erythropoietin level $< 100$ mU/mL and a Hb rise of $> 0.5$ g/dL are likely to respond (Ludwig et al, 1994). Serum erythropoietin is not routinely assessed in clinical practice and therefore of limited value. Roche do provide a predictive marker service “free of charge…as a service to medicine”.

3.2 Overall survival

19 studies (2865 participants) assessed within the Cochrane Review assessed survival. RHuEPO was shown to significantly improve overall survival in cancer patients with a hazard ratio of 0.81 (95% CI 0.67 to 0.99). However a single study (Littlewood et al, 2001) contributed more than 50% of the patients analysed within this result, and when excluded from analysis, the result was no longer statistically significant. Based on this data the review concludes that there is “suggestive but inconclusive evidence for a positive effect of erythropoietin on overall survival”.

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However it is important to appreciate that none of the studies within the Cochrane Review were designed to test for overall survival as the primary endpoint. The Littlewood study amended the protocol to prospectively collect survival data whilst the study was running. In addition, recent studies of erythropoietin, with survival as the primary end-point, in advanced head and neck cancer (Henke et al, 2003) and the BEST study in breast cancer (Leyland-Jones, 2003; FDA, 2004) have demonstrated a negative effect on survival.

3.2.1 Comment

It is extremely important to consider why these recent studies have demonstrated an adverse effect on outcome and survival and the impact this may have on the use of rHuEPO in routine clinical practice.

Unlike the Littlewood study, which dominated the Cochrane Review of survival, both of the more recent studies offered erythropoietin to patients with a relatively high Hb concentration. It has been speculated that the use of erythropoietin in patients with relatively high Hb concentrations may be associated with a higher incidence of serious adverse events.

In vitro data does suggest a potential mechanism by which rHuEPO may lead to an adverse effect on survival. Expression of erythropoietin receptors has been identified on cancer cells and it has been speculated that activation of these receptors may protect the tumour cell from apoptosis. Indeed, in vitro data exists which demonstrates that tumour cells treated with erythropoietin become more resistant to subsequent treatment with chemotherapy.

In summary, the survival data regarding erythropoietin is unclear. Although the Cochrane Review suggests a small but insignificant benefit, more recent data suggests an adverse effect on survival. It is essential that further studies, specifically designed to assess the effect of erythropoietin on survival be performed. In addition, two recent studies published suggest it may be unwise to treat patients with erythropoietin for mild anaemia (Hb 10 to 12 g/dL). It may also suggest that it is inappropriate at present to use rHuEPO for the treatment of cancer related anaemia in patients who are receiving curative treatments i.e. patients with testicular cancer, adjuvant breast chemotherapy and many paediatric patients.

3.3 Quality of Life

14 studies (2113 participants) assessed changes in quality of life parameters. Although many individual studies have reported an improvement in quality of life offered by the use of rHuEPO, the Cochrane Review concluded that the results of the available studies “were inconsistent with respect to the effects of erythropoietin on quality of life and fatigue.”
Following the Cochrane Review, a number of clinical trials have reported improvements in QoL with rHuEPO (Fallowfield et al, 2002; Cella et al, 2003; Littlewood et al, 2003).

### 3.4 Adverse events

Adverse events associated with erythropoietin commonly include flu-like symptoms with headaches, joint pains, weakness, dizziness and tiredness, side effects that most often occur at the start of treatment.

Other more significant side effects were formally assessed within the Cochrane Review.

1) **Thrombotic events** (thrombosis or related complications such as transient ischaemic attacks, stroke, pulmonary embolism or myocardial infarction) appeared more frequent in patients treated with erythropoietin. However with a relative risk of 1.58 (CI 0.94 to 2.66, 12 trials, n=1738) the Cochrane Review concluded that there is insufficient evidence to conclude that erythropoietin increases the risk of thrombotic events. An excess number of thrombotic events has recently led to the early termination of a trial of Eprex® in patients with metastatic breast cancer (Rosenzweig et al, 2004).

2) **Hypertension.** The relative risk to develop hypertension for erythropoietin treated patients was increased by 19% (relative risk 1.19; 95% CI 0.96 to 1.49, 12 studies, n=1656), a result that does not achieve statistical significance.

3) **Haemorrhage/Thrombocytopenia** - non-significant increase in the relative risk of haemorrhage or thrombocytopenia (relative risk 1.26, 95% CI 0.85 to 1.86, 8 trials, n=1082).

4) **Rash, irritation, pruritis.** 21 events in 675 patients in 8 trials with of skin rash, irritation, giving a relative risk of 1.17 (95% CI, 0.63 to 2.18) again insufficient evidence to conclude that erythropoietin increases the risk of skin reactions.

5) **Seizures.** 3 studies including 389 participants reported the incidence of seizures with no significant differences between the groups compared.

#### 3.4.1 Pure red cell aplasia

An additional adverse event that has received particular attention is pure red cell aplasia (PRCA). This is caused by the development of neutralising anti-EPO antibodies that cross-react with all currently available erythropoietic agents (epoetin alfa and beta, and darbepoetin alfa), and endogenous erythropoietin. The majority of cases have been associated with epoetin alfa and almost exclusively in patients with chronic renal failure on haemodialysis. A
recently published study (Bennett et al, 2004) reported 175 cases of pure red-cell aplasia associated with Eprex® and 11 with NeoRecormon® from January 1998 and April 2004. It would appear that this effect relates to other factors within the preparation as the incidence of PRCA Eprex® formulation without human serum albumin was estimated to be 18 per 100,000 patient-years, but 6 per 100,000 patient-years for an Eprex® formulation containing albumin (compared to 1 case per 100,000 patient-years for NeoRecormon®)

3.4.2 Comment

The Cochrane review did not identify any serious adverse event increased (with statistical significance) by rHuEPO. However, more cases of hypertension and thrombotic adverse events are reported in many of the studies. It is therefore prudent to follow the prescribing information for all of the rHuEPOs and avoid use of the agent in patients with uncontrolled hypertension. The use of rHuEPO in patients with active thrombo-embolic disease or unstable angina may also be considered unwise.

4 Conclusion

- Anaemia (Hb < 12 g/dL) is frequently associated with cancer and is a cause of significant morbidity to many patients and has a negative impact on their quality of life.

- Patients who become anaemic are often treated with blood transfusions, but their use is often delayed until the patient becomes markedly symptomatic suggesting current standards of care may be inadequate.

- The routine use of blood transfusion in all patients with cancer-treatment related anaemia would have a significant and possibly unsustainable impact on the transfusion services and cancer centres.

- Strong evidence exists regarding the efficacy of rHuEPO with respect to both haematological response and a reduction in the number of blood transfusions required. Recent data are persuasive for a positive effect on QoL. Data regarding the effect on survival is more controversial and further studies are required.

- RHuEPO should be used in patients with moderate anaemia (≤ 11 g/dL) before or during chemotherapy. In patients with evidence of iron deficiency (serum ferritin ≤ 450 pmol/L or ≤ 675pmol/L with transferrin saturation ≤ 19%), the role of concomitant IV iron should be strongly considered. Treatment should be continued
for four weeks after the last chemotherapy. Patients in whom the Hb increase is ≤ 1 g/dL within the first four weeks are unlikely to respond.

- All three rHuEPO agents are effective. Little data exists to allow an informed choice between them based on efficacy. Toxicity also appears to be broadly similar. PRCA more frequent with Eprex® is less common with modern preparations and should be considered a rare complication. Dosing schedules are different and this may guide choice of agent by patient preference.

- There is some concern regarding the effect of rHuEPO on survival. It should therefore be considered unwise to propose the unrestricted use of erythropoietin in the treatment of cancer related anaemia. A sensible compromise would be to propose the use of recombinant erythropoietin in patients receiving palliative treatment in whom small negative effects on overall survival may be appropriately balanced with improvements in symptom control and quality of life.
5 References


