Epoetin (alfa and beta) and darbepoietin alfa in patients with cancer treatment induced anaemia:

**Background.**

Naturally occurring erythropoietin is a glycoprotein manufactured in peri-tubular renal fibroblasts. Erythropoietin production is stimulated by tissue hypoxia mediated via hypoxia inducible factor. In patients with renal failure there is sub-optimal production of erythropoietin and anaemia is very common. Recombinant erythropoietin (rHuEpo) was developed in the early 1980s and clinical trials in anaemic patients with renal failure showed that rHuEpo was very effective at correcting anaemia, abolishing transfusion need and improving quality of life. Some patients did not respond to treatment or lost their response after a period of treatment. Common explanations for a lack of response were the development of iron deficiency or co-existent infection or inflammation. Intravenous iron is now routinely given to all patients with renal failure receiving rHuEpo which helps to prevent iron deficiency and also allowed an approximately one third smaller dose of rHuEpo to be given. Hypertension and thrombosis were quite commonly seen in the early days of treatment with rHuEpo but these side effects have diminished in importance as renal physicians have got used to increasing the haemoglobin concentration more slowly and pick up and treat complications such as hypertension early. About 5 years ago pure red cell aplasia was noted in some patients taking rHuEpo. This potentially life threatening side effect was predominantly seen in Europe in patients receiving epoetin alfa by the sub-cutaneous route. Investigation has suggested that a change in the formulation of epoetin alfa was responsible and this problem now seems to have been corrected. At its peak incidence this remained a rare complication (<1/10,000) patients but potentially very serious. Many of the affected patients have improved after withdrawal of rHuEpo and immunosuppressive therapy.

**RHuEpo in patients with cancer**

**Cause of Anaemia**

Anaemia is a common problem in patients with cancer. Depending on tumour type and treatment at least one third to one half of patients with cancer will be anaemic at some point during their illness and for many types of cancer the incidence of anaemia is much higher. Anaemia may be caused by bleeding, iron deficiency or haemolysis but in the large majority of patients the anaemia will be attributed to the cytokine driven anaemia of chronic disease compounded by the myelotoxic impact of the patient’s treatment with chemo and or radiotherapy.
Impact of anaemia

Anaemia may cause many symptoms such as fatigue, breathlessness, swollen feet, chest pain and inability to concentrate. Fatigue is reported to be the single most important symptom experienced by patients with cancer and now leads the list of patient concerns ahead of other important problems such as pain and nausea. Fatigue may be caused by many factors, both physiological and psychological and anaemia is just one of the possible causes. Nevertheless, it is a potentially correctable cause.

Treatment with rHuEpo

Recombinant erythropoietin was first used in the treatment of anaemia in patients with cancer in around 1990 when Professor Ludwig reported a study in 13 patients with myeloma. Since then many studies (both phase II and III) have been reported. Although there were differences in the design of these studies, in the nature of the patients recruited and in the brand of erythropoietin used, the authors were able to draw some quite similar conclusions. Firstly, they were able to show that rHuEpo increased the haemoglobin by more than 2.0g/dl in around 45-70% of patients. This rather arbitrary definition of response has been used in most studies and perhaps slightly underestimates the number of patients who benefit. For example, a patient whose haemoglobin increased by 1.5g/dl may well have important clinical improvement but would be classed as a non-responder. The improvement in haemoglobin resulted in a 20-50% reduction in the number of units of red cells transfused.

Impact on quality of life

Perhaps most importantly, patients who responded to treatment were shown to have an improvement in their quality of life when measured using a variety of scales such as the cancer linear analogue scale, the FACT-An and short form 36. One study, using darbepeoietin, also showed that patients who felt physically better had an improvement in their mental health measured using the Brief Symptom Inventory. I have a number of patients who illustrate exactly what impact anaemia correction can have on quality of life and what it can not do for them. Correcting anaemia makes many patients feel better. On the linear analogue scale, for example, they might score themselves at 40 (out of 100) pre rHuEpo and 60 after anaemia correction. A normal person typically scores themselves between 70-90. In other words, correcting anaemia improves patients’ sense of well-being but does not often return them to normal. They still have cancer and they are still receiving chemotherapy both of which are likely to adversely affect their health. Importantly, work by David Cella has shown that the improvement in quality of life is of clinical importance to the patients. Given the dangers of trying to compare different products by comparing their results when used in differing patient populations there does not seem to be evidence of superiority for one
erythropoietin over another in terms of effectiveness. Darbepoietin, with its approximate three-fold longer half life, might have an advantage because of less frequent dosing.

Side effects

Most of the studies have reported few side effects attributable to rHuEpo. Hypertension is only slightly more common in rHuEpo treated patients compared to those receiving placebo. Thrombotic problems (venous and arterial) occur slightly more commonly in rHuEpo treated patients. A recent review suggested a 1.5 times increased risk of thromboembolism in treated patients. Pure red cell aplasia has not been reported in patients treated for cancer related anaemia.

Impact on life expectancy

The question of whether treatment with rHuEpo has an effect on life expectancy is controversial. There are some theoretical reasons why there may be a positive effect; increasing haemoglobin concentration increases tissue oxygen delivery and may reduce tumour hypoxia. Tumour hypoxia may result in increased angiogenesis and an increase in malignant potential. Also, hypoxic tumours may be less sensitive to treatment with radiotherapy and chemotherapy so anaemia correction might be beneficial. In contrast, there have been some concerns that treatment with rHuEpo might directly stimulate tumour growth and might have a stimulating effect on vascular endothelial cells leading to increased angiogenesis. The clinical trials conducted to date have produced a mixture of results related to survival. A summary to date would be that there is no evidence either for a positive or negative impact of rHuEpo on tumour response nor survival.

Prediction of response

Because around 40% of patients do not respond to rHuEpo it would be helpful if we could predict those patients who were most likely to respond. Low baseline serum erythropoietin levels and a normal platelet count have been suggested to be positive factors for response. However, there is no single or combination of factors which are sensitive and specific for response to rHuEpo. The development of iron deficiency and co-existent infection or inflammation can block response as they do in patients with renal failure. Iron replacement is important when appropriate. Whether this should be given intra-venously or orally is uncertain at the moment although there are two recent studies which support the role of the intra-venous form.
**RHuEpo in patients not currently receiving chemotherapy**

There are just a few studies in this area. In brief, patients with cancer related anaemia that have previously received or never previously received chemotherapy, respond to treatment with RHuEpo in a similar manner to those patients currently on active treatment.

In some patients anaemia is the only manifestation of their illness causing symptoms and giving chemotherapy in an attempt to correct the haemoglobin is not always appropriate. Such patients can do very well on treatment with rHuEpo. I have a number of patients (particularly with CLL) who, I think, have been saved from the need for chemotherapy by the use of rHuEpo. A study by Pangalis in 2002 suggested that rHuEpo can ‘down stage’ patients with CLL and, again, makes the point that patients can have treatment with chemotherapy postponed.

**RHuEpo in patients anaemic after a bone marrow transplant**

After autologous or allogeneic stem cell transplant treatment with rHuEpo can reduce transfusion need (more after allogeneic than autologous transplant) but the impact is relatively small for most patients and I have not used rHuEpo to any extent in this setting.

**Conclusions**

Treatment with rHuEpo is a proven method of increasing the haemoglobin concentration, reducing transfusion need and improving quality of life in anaemic patients with cancer. Some patients will benefit a lot from treatment, some a moderate amount and others obtain little or no benefit. Large randomized trials have shown that rHuEpo is safe with, probably, just a small excess of thrombotic events induced by treatment. There is no convincing evidence that rHuEpo either improves or decreases survival in patients with cancer.

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