Treating anaemia: damned if you do, damned if you don’t

Mary Rice

Many cancer patients suffer unnecessary levels of fatigue due to a failure to treat their anaemia. But just as the cost of erythropoiesis-stimulating proteins looks set to fall, surprise research results are prompting questions over whether these drugs might actually be stimulating tumour growth.

Until recently, epoetin, the human recombinant form of erythropoietin, was considered by most oncologists to be of considerable benefit for patients suffering from cancer-related anaemia. When used in this way it improves red blood cell levels and hence reduces fatigue, one of the most common and debilitating complaints of cancer patients. It all seemed fairly obvious: the literature showed that a low haemoglobin count is associated with poor outcomes in such patients, and increasing the haemoglobin can significantly improve quality of life. Improving the quality of life generally has some bearing on survival and disease progression in cancer patients, and no-one had any serious worries about this subject.

That was until the publication of two studies that appeared to show that patients taking erythropoiesis-stimulating proteins (ESPs) had worse outcomes in terms of survival. The results were unexpected, not least for the investigators, and prompted many to wonder whether the established view of ESPs was correct.

In 2003, Michael Henke, from the University Hospital, Freiburg, Germany, and colleagues, published a study which showed results that surprised both the authors and fellow oncologists (Lancet 2003, 362:1255–60). They ran a multicentre, randomised, placebo-controlled trial in 351 patients with low haemoglobin levels who suffered from head and neck cancer. All the patients given epoetin β had considerable improvements in their haemoglobin levels compared with those who were on placebo. This was as expected. But what came as a shock to Henke were the findings on disease control and survival – in both cases the outcomes were worse in the ESP group. “Despite a reliable rise in haemoglobin concentrations, we saw no benefit for locoregional progression-free survival, locoregional disease control or overall survival,” argues Henke. “In fact, there was a trend towards an increased rate of locoregional recurrence in patients treated with epoetin β.” When Henke’s team examined the patients’ tumours, they found that the ESP had increased the proliferation of cancer cells. It seemed that the ESP was stimulating the tumour growth.

The results of another study by the same team, this one in patients with rectal cancer, were even more surprising. They found that combination chemotherapy and epoetin β led to a much poorer outcome than chemotherapy alone. The ESP was associated with increased tumour growth, likely due to the increased production of growth factors by cancer cells.

Michael Henke: findings were the opposite of what we expected. We are waiting anxiously for our next results.
progression, or survival,” said the authors. “On the contrary, patients given placebo fared significantly better than those given epoetin β. A contribution of study design to this unexpected finding is unlikely.”

**SURPRISE RESULTS**

“We knew that patients who had hypoxia didn’t react as well to radiotherapy as those who didn’t,” says Henke. “There is pre-clinical evidence that epoetin increases the radiosensitivity of tumours, and we thought it would therefore improve the efficacy of radiation and chemotherapy. We therefore believed that patients with anaemia undergoing radiotherapy would benefit from having their haemoglobin levels boosted with epoetin. So we were expecting just the opposite results from those we found, which really surprised and disappointed us.”

Imbalances with certain subgroups in the trial might have contributed to the negative effect of the drug on outcomes, says the paper, but underlying biological phenomena are also a possibility. Further trials are needed, says Henke, to try and explain the biological mechanism that might underpin the findings, and he is currently looking further into the possibility that tumour cells in some kinds of cancers may express erythropoietin receptors and that they use the erythropoietin system for growth and angiogenesis. If this is the case, he says, the finding could have considerable clinical benefit. “You could look for ways of blocking epoetin expression in the cells and thereby improve results, as well as giving doctors a new way of predicting outcomes more accurately.”

Henke’s study has, perhaps predictably, come under considerable fire regarding its design, results, and interpretation. He takes a sanguine view. “When you do research and make an unexpected observation you expect to get criticism. However, I would say to critics that there is no good clinical study that shows that what we have found is wrong. Most previous ESP studies have focussed on quality of life in palliative treatment. We wanted to see if it would heal rather than ameliorate. Another difference is that ESPs have previously been studied mainly in patients with disseminated disease, who would probably have died anyway, whereas we were looking at people with localised cancers in the hope that we could make them well. As far as we are aware, ours is the only properly designed study to look at these issues. We are waiting anxiously for our next results.”

The study supports findings from another study of epoetin use (epoetin α) in breast cancer (Leyland-Jones, *Lancet Oncology* 2003 4:459–460). In this trial, the treatment group was observed to have an increased incidence of disease progression compared with the placebo group, and the outcome was higher mortality in the treatment group.

In the light of these studies, last year the US Food and Drug Administration (FDA) convened a panel to scrutinise safety. A spokesman said: “FDA is currently working with sponsors of approved and investigational erythropoietin products to ensure that studies are conducted to investigate possible impact of the drug on tumor growth promotion. Separate from the meeting last May, the product labelling for the erythropoietin products approved in the US (EpoGen [epoetin α], Procrit [epoetin α], and Aranesp [darbepoetin α]) have been updated to reflect this new information and revised labelling has been distributed under the cover of Dear Health Care Professional letters to the medical community.” The European Medicines Agency (EMEA) currently has no plans to undertake an investigation of its own, and will await the outcome of further studies. So it appears that the jury is still out on this issue.

Amgen, which manufactures Aranesp, said it could not comment on other companies’ studies. However, Amgen’s European Medical Director, Dietmar Berger, said the company was keeping a close eye on the situation: “Amgen has a robust pharmacovigilance programme that is evaluating the effect of Aranesp on survival and tumour progression in multiple oncology populations with well-designed clinical and epidemiological studies.”

He also pointed out that the drug served a real need: “Cancer patients cite anaemia as one of the most debilitating side-effects of chemotherapy. When used in accord with the approved prescribing guidelines, Aranesp effectively corrects anaemia and reduces or eliminates the need for blood transfusions in chemotherapy patients, without the burden of frequent injections and doctor’s office visits.”

**A REAL NEED**

There is no doubt that anaemia is a problem for cancer patients. Heinz Ludwig, from the Wilhelminenspital, Vienna, Austria, and colleagues from all over Europe, collected data on cancer-related anaemia from 748 cancer patients...
centres in 24 countries over a six-month period in 2001 (EJC 2004, 40:2293–2306). This large study showed clearly that anaemia prevalence and incidence among cancer patients were high, and that anaemia had a strong relationship to poorer outcomes. Treatment for anaemia may not be optimal, say the authors: many anaemic patients, including those with very low haemoglobin levels who fall into the category where they should be treated under existing guidelines, were not treated at all. Of all patients who were ever anaemic, 61.1% did not receive treatment for their anaemia.

Most patients who were not treated had haemoglobin levels that were too low, but not disastrously so – 47.2% of those not treated had levels between 10.0 and 11.9 g/dl; but 12.9% who were not treated had levels between 8 and 9.9 g/dl; and 0.9% were below 8 g/dl.

Most patients who began chemotherapy during the study became anaemic. The longer they received chemotherapy, the greater their risk of developing anaemia: it was reported in 19.5% of patients in the first chemotherapy cycle and 46.7% in the fifth cycle. Even in the anaemic group with the highest levels of haemoglobin (10–11.9 g/dl) their anaemia had a significant impact on performance status. Using the physician-reported WHO score, it was shown that performance status worsened as haemoglobin decreased, and the correlation was significant. Over half the patients with severe anaemia (haemoglobin less than 8 g/dl) had poor scores, and even among those with haemoglobin levels of 10–11.9 g/dl, one quarter had poor scores. This association is consistent with findings that show a correlation between increasing haemoglobin and quality of life, the study said.

“From the biological point of view it’s...
EORTC Guidelines for use of erythropoietic proteins in anaemic patients with cancer

Anaemia is a frequent finding in cancer patients and should be carefully assessed. Additional causes of anaemia such as iron deficiency, bleeding, nutritional defects or haemolysis should be corrected prior to erythropoietic protein therapy. The following recommendations are related to adult cancer patients with solid tumours or haematological malignancies:

- In cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90–110 g/l based on anaemia-related symptoms.
- In patients with cancer-related anaemia not undergoing chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90–110 g/l based on anaemia-related symptoms.
- Erythropoietic proteins may be considered in asymptomatic, anaemic patients with a Hb level of 90–110 g/l to prevent a further decline in Hb, according to individual factors (e.g., type/intensity of chemotherapy, baseline Hb).
- For anaemic patients who are transfusion-dependent, erythropoietic proteins should be initiated in addition to red cell blood transfusions.
- We do not recommend the prophylactic use of erythropoietic proteins to prevent anaemia in patients undergoing chemotherapy and/or radiotherapy who have normal Hb values at the start of treatment.
- Elderly patients experience the same benefits from treatment with erythropoietic proteins as younger patients.
- The target Hb concentration should be 120–130 g/l.
- The two major goals of erythropoietic protein therapy should be to improve quality of life and prevent transfusions.
- The use of erythropoietic proteins with the aim of improving survival or response to treatment is not recommended as there is no evidence to support this. Further studies are needed.
- Within reasonable limits of body weight, fixed doses of erythropoietic proteins should be used.
- We recommend the dosing of erythropoietic proteins according to Fig. 1. However, the decision to dose-escalate cannot be generally recommended and must be individualised. Treatment should be continued as long as Hb levels remain ≥120–130 g/l and patients show symptomatic improvement. For patients reaching the target Hb, individualised titration of lowest effective maintenance dose should be made repeatedly.
- Despite the common use of epoetin α QW (40,000 IU), there is limited evidence to support this dosing.

However, guidelines by their very nature are fairly general – if they are not, they are just too complicated for anyone to follow, and they are bound to end up as a compromise.”

As to the effect of ESPs on survival, Ludwig and colleagues did not see a negative impact. However, there may be sub-groups where they should be used with caution, he says. “In patients with solid tumours and high tumour mass or people who were incompletely resected, we should probably be careful about recommending ESPs, but in other groups we should exploit their benefits,” he says.

A Cochrane systematic review of the effect of ESPs used to prevent or treat anaemia in cancer patients was updated in May 2004, after the publication of the two studies causing concern (Bohlius et al, The Cochrane Database of Systematic Reviews 2004, 3: CD003407.pub2). The authors found consistent evidence that ESP administration reduces the risk for blood transfusions, and that for patients with haemoglobin levels below 10 g/dl...
The QW administration of darbepoetin α (2.25 µg/kg) can be recommended. There is currently limited evidence to support the use of darbepoetin α in Q2W, Q3W or Q4W dosing intervals.

The use of higher initial doses of erythropoietic proteins can currently not be recommended as a standard approach with epoetin α or epoetin β, but limited evidence exists for darbepoetin α. Further studies are needed.

There are no predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice; a low serum erythropoietin 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.

For patients undergoing autologous blood stem cell transplants, the effects of erythropoietic proteins have not yet been convincingly shown and they cannot therefore be recommended.

For patients undergoing allogeneic blood stem cell transplants, the clinical impact of erythropoietic proteins is limited and they can only be recommended on an individual basis.

The fear of pure red cell aplasia should not lead to erythropoietic proteins being withheld in patients with cancer.

When using erythropoietic proteins to treat anaemia in cancer patients, the combined analysis of all study data indicates a slightly increased risk of thromboembolic events. However, this may be related to the target Hb level achieved.


Jan Foubert: Anaemia-related fatigue is a heavy burden for cancer patients. We shouldn’t jump to conclusions.

Jan Foubert, President of the European Oncology Nursing Society, who runs a specialist fatigue clinic at the Institut Bordet in Brussels, Belgium, says that ESPs are helpful in boosting energy levels and controlling fatigue in the patients he sees. “In studies of anaemia in cancer patients, we see improvement in the haemoglobin levels when they take ESPs.” He adds, however, that there is a need for more research into the link between fatigue and anaemia especially in elderly cancer survivors. Research is also needed into the link between fatigue and depression, anxiety and sleep disturbance, and into how activity may help in managing fatigue.

Foubert worries that the results of the Henke and Leyland-Jones studies may hinder attempts to get the problem of anaemia in cancer patients taken more seriously and dealt with more consistently. “The significance of anaemia and fatigue to the patient is
often overlooked in routine assessments, and optimal methods for assessing and treating these conditions remain unclear,” he said. He is confident that treating anaemic patients with ESP helps their quality of life, and feels that there were probably problems in the design of the studies that showed worse outcomes. “We shouldn’t jump to conclusions. New guidelines are very careful about the target level, the duration and follow-up of treatment, and the endpoints.”

**Falling prices**

One of the reasons why ESPs are not used more widely to treat anaemia in cancer patients is cost. In Italy, for example, the national health service will reimburse ESP treatment for only a small and limited group of patients – anaemic patients with chronic renal failure undergoing dialysis, and cancer patients suffering chemotherapy-associated anaemia. Yet in 2001 ESPs ranked fifth in terms of total out-of-hospital expenditure on drugs by the Italian national health service, accounting for 209 million euros, or 1.7% of total drug expenditure.

The high prices make ESPs a major earner for the industry; according to the IMS World Review, they ranked seventh in global sales figures for 2003, coming in at $10.1 billion, after cholesterol and triglyceride reducers, antilcerants, antidepressants, antirheumatic non-steroids, antipsychotics and calcium antagonists (plain). However, this may now be set to change, and Ludvig argues that price cuts and the advent of biosimilar drugs will mean that epoetin will soon become a standard treatment for cancer-related anaemia. The problem is, given the question marks thrown up by the results of recent trials into the impact of ESPs on tumour progression and survival, which patients stand to benefit and which to lose?

Giovanni Apolone of the Istituto Mario Negri, Milan, Italy, recently wrote an editorial on the subject for the European Journal of Cancer (vol 40:1289–1291). He believes existing guidelines issued by regulatory authorities are sound. “Within the indications of the FDA, EMEA and other international and national regulatory agencies, at present ESPs should be considered a class of drugs that has received a quite complete assessment in terms of risk-benefit analysis. Several systematic reviews and meta-analyses support these indications. Basically, although some differences do exist between countries, the use of ESPs in patients with cancer to treat or prevent anaemia secondary to cancer or resulting from its treatment is recommended for treatment in patients with severe anaemia, as an alternative to blood transfusion. In less severe anaemia, the decision to give epoetin should be determined by a careful examination of the clinical circumstances,” he says.

To address this situation, EORTC have recently produced a set of guidelines for ESP use in cancer patients (see pp 18, 19).

He adds, however, that the unexpected correlations found between ESPs and worse prognosis in the two studies on head and neck cancer and breast cancer show the need for further research. “We need to carry out more studies in the light of such unexpected results as Henke’s. These should either be entirely new or re-evaluations of old studies in order to have a better understanding of the reasons for these results. These could be due to the expression of biological factors regulating or modulating the clinical expression of these drugs, and we need to know if they exist and what they are.

“There is some pre-clinical evidence that some cancers (breast, prostate, and ovarian) possess erythropoietin receptors and that these cells may proliferate in response to epoetin use, but there are other cancers, such as small cell lung cancer, where this phenomenon could not be demonstrated. What is needed is translational research to confirm results from these pre-clinical studies in randomised clinical trials in a homogenous population, and with an accurate and systematic collection of information that allows for stratification of subjects in various categories according to receptor status (presence and quantities).”

Until further trials are done, says Apolone, we cannot know whether the guidelines need to be amended, and he urges the industry to focus on this task. “Pharmaceutical companies marketing variants of epoetins worldwide, instead of arguing about the internal and external validity of available evidence from controlled clinical trials, should facilitate and support new pre-clinical studies to discover the biological basis of the unexpected clinical results.” In the meantime, he says, the use of ESPs outside the existing guidelines should be considered only in the context of very well planned and carefully monitored clinical studies that implement strict ethical safeguards for patients.