Recombinant human erythropoietin in oncology: current status and further developments

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Received 29 July 2004; revised 17 January 2005 and 23 March 2005; accepted 12 April 2005

Anaemia effects up to 90% of cancer patients, with more than 60% requiring blood transfusion during or after treatment. With the advent of recombinant human erythropoietins (rHuEPO), an alternative to red blood cell transfusion has become available. So far, three drugs have been approved for the treatment of anaemia in patients with malignancies (epoetin alfa, epoetin beta and darbepoetin alfa). New concepts for the use of erythropoietin in cancer patients include 3- and 4-weekly dosing, as well as loading-dose concepts. Important factors helping to judge the impact of erythropoietin in cancer treatment include pharmacoeconomics and better predictive factors. Lately, the influence of erythropoietin therapy on survival in cancer patients has been discussed very intensively, because conflicting data have emerged. Studies aimed at correcting anaemia in cancer patients had indicated a possible survival advantage of those patients receiving erythropoietin. In contrast, two recent trials aimed at correction of haemoglobin levels beyond anaemia reported a poorer survival of patients receiving erythropoietin. This might grossly be attributed to a higher risk of thrombosis in these patients. The largest systematic review on the use of erythropoietin in cancer patients undergoing treatment indicates a suggestive but not significant survival advantage of erythropoietin-treated patients. In addition, very recent results of a Food and Drug Administration meeting on safety and survival of patients treated with erythropoietin are presented.

Key words: anaemia, cancer, darbepoetin alfa, erythropoietin

Introduction

Anaemia, clinically defined as a haemoglobin (Hb) level <12 g/dl, is the most predominant haematological disorder in cancer patients. Depending on the tumour type, the incidence of anaemia at the time of diagnosis ranges from 20% to 60% [1]. In addition, myelosuppressive chemo- and radiotherapy can induce anaemia or aggravate that which already exists [2, 3]. Besides the overall quality of life (QoL), low Hb levels may negatively influence the patients physical performance [4, 5].

Although the use of red blood cell (RBC) transfusions is still quite common for the treatment of anaemia, this therapy has a number of drawbacks. Even today the risk of transmission of viral and bacterial infections cannot be ruled out. In 256 reports of transfusion-associated death received by the United States Food and Drug Administration (FDA) between 1976 and 1985, the majority (51%) were caused by acute haemolysis due to ABO incompatibility. Other causes included pulmonal injury, delayed haemolysis, bacterial infections and graft-versus-host reactions [6]. Transfusions can also cause immune suppression [7].

With the introduction of human recombinant erythropoietin (rHuEPO) in oncology about 10 years ago, an alternative to RBC transfusion became available [8]. In addition to improving symptoms of anaemia, the use of erythropoietin might also influence overall QoL and the prognosis of patients. In order to give a framework for erythropoietin therapy, the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) and, more recently, the European Organisation for Research and Treatment of Cancer (EORTC) developed evidence-based guidelines on the use of epoetin in cancer patients [9, 10].

To increase treatment efficacy and to improve patient compliance, a number of different administration regimes for rHuEPO are currently under evaluation, including less frequent dosing and loading-dose concepts. In addition, with the development of darbepoetin alfa, a genetically modified erythropoietin with longer half-life has become available [11]. Owing mainly to economical considerations, the general use of recombinant erythropoietin has not become common practice in the oncological setting.

Erythropoietin: mechanism of action

Synthesised in the kidney and to a minor degree in the liver, erythropoietin is the primary regulator of human erythropoiesis.
The native glycoprotein hormone has a molecular weight of 34 kDa and consists of 165 amino acids. About 40% of the molecular mass is composed of carbohydrates [12]. Glycosylation itself does not influence the biological activity, but delays the clearance of the hormone from the plasma [13]. Particularly important in this aspect are the sialic acid residues bound to four of the carbohydrate hydrate side chains, leading to a biological half-life of the molecule of $\approx 8.5$ h [14].

In response to a decrease in tissue oxygenation, erythropoietin is released into the plasma and binds to erythropoietin receptors on the surface of red-blood cell precursors (BFU-e, CFU-e, erythroblasts) located in the bone marrow. As well as prolonging their survival, erythropoietin inhibits apoptosis of the precursor cells, thereby inducing their proliferation and differentiation [15].

**Causes of cancer-related anaemia**

Anaemia in patients with malignancies is caused by factors related to the disease itself and by the myelosuppressive and nephrotoxic effects of certain cancer therapies [16–18]. Tumour-associated factors can be acute or chronic tumour bleeding, haemolysis, deficiency in folic acid and vitamin B_{12}, as well as infiltration of the bone marrow. Immune cell activation triggers the release of several cytokines, affecting the proliferation of progenitor cells or the production of erythropoietin. Tumour necrosis factor-$\alpha$ secreted by monocytes and macrophages, for example, stimulates the production of interferon-$\beta$ in stromal cells of the bone marrow, inhibiting the proliferation of the erythroid precursors BFU-e and CFU-e. In addition, activation of macrophages can lead to a shorter erythrocyte half-life and to a decrease in iron utilisation. Released cytokines also inhibit the production of erythropoietin in the kidney, resulting in relatively low levels of the hormone, compared with the grade of anaemia observed (Figure 1, pathophysiology of anaemia).

Depending on the drug and schedule used, cytostatic therapy has a major impact on the incidence of anaemia in cancer patients [2, 3]. Contributing factors include the inhibition of erythropoietin production by nephrotoxic platinum compounds and the myelosuppressive effects on the erythroid precursor cells. Dose-intensified treatment regimes or shortened treatment intervals, as well as multimodal therapies, are associated with a higher degree of anaemia. In addition, some of the newer chemotherapeutic agents such as taxanes or vinorelbine are strongly myelosuppressive and cause high degrees of anaemia [3]. Some groups of cancer patients show particularly high incidences of anaemia during or after cytotoxic therapy. This is the case for $\approx 70\%$ of myeloma patients and $\approx 50\%$ of lung and ovarian cancer patients [19]. Anaemia is also frequently observed in patients with head and neck tumours, breast cancer, genitourinary tumours and lymphomas [3].

**Symptoms of anaemia**

Anaemia can affect most organs of the human body. Besides psychological effects that may lead to social isolation and depression, there are a number of physical symptoms including
dyspnoea, tachycardia, dizziness or vertigo, cardiac hypertrophy, low skin temperature, impaired cognitive function, anorexia, and nausea [20]. In this context it is also noteworthy, that a decline in Hb of >2 g/dl is correlated with a significant reduction in the Karnofsky index [21].

One of the most common anaemia-related problems is fatigue, a condition of exhaustion that cannot be improved by rest or sleep, impairing the patient’s ability to perform normal daily activities. Studies have shown that 60% to 96% of patients undergoing chemotherapy suffer from this syndrome [22].

Recombinant human erythropoietins

Three recombinant erythropoietins have been approved for the treatment of anaemia in cancer patients: epoetin alfa, epoetin beta and darbepoetin alfa. Epoetin alfa and darbepoetin alfa are approved for patients with solid tumours and non-myeloid malignancies under chemotherapy in general. The indication for epoetin beta is restricted to patients with solid tumours undergoing platinum-containing chemotherapy [23–25].

Like the native hormone, epoetin alfa and beta consist of 165 amino acids, but differ in their carbohydrate content, owing to differences in production and purification. After subcutaneous injection, which is the method of choice in cancer patients, epoetin alfa and beta have an average half-life of 8 h. The recently developed darbepoetin alfa has a higher molecular weight of ~38 kDa. This is due to the fact that five amino acids have been exchanged by site directed mutagenesis, leading to two additional N-glycosylation sites, thereby increasing the number of sialic acid residues from ≤14 to ~22. This modification leads to a longer terminal half-life of ~49 h after subcutaneous injection, but resulted in a lower receptor binding capacity leading to lower biological activity in vitro [25, 26].

In addition to the standard regimen of 10 000 IU or 150 IU/kg thrice weekly, epoetin alfa and beta are also being administered once weekly. The recommended dose for darbepoetin alfa is 2.25 µg/kg per week [23–25].

Treatment of cancer-related anaemia with erythropoietin

Over the recent years, many controlled randomised studies have shown the efficiency and tolerability of rHuEPO for tumour- as well as for chemotherapy-induced anaemia (Table 1) [27–42].

With response defined as an increase in Hb of >2 g/dl or the restoration of transfusion independence, response rates of 32% to 82% were reported, depending on the type of treatment and the underlying disease. These studies have also shown that the number of RBC transfusions could be significantly reduced. These data are exemplified in a study by Littlewood et al. [39], who investigated the efficacy of epoetin alfa on transfusion needs and QoL in 375 patients suffering from solid or
non-myeloid haematological malignancies treated with a non-platinum-based chemotherapy. Randomised 2:1, patients with an initial Hb level of ≤10.5 g/dl or with a decrease in Hb of ≥1.5 g/dl per chemotherapy cycle received epoetin alfa (150 IU/kg three times per week, subcutaneously) or placebo. The treatment was given for 12–24 weeks during chemotherapy and then for an additional 4 weeks. While the mean Hb level in the epoetin group showed an increase of 2.2 g/dl, the average increase for placebo was 0.5 g/dl (P <0.001; Figure 2).

Compared with patients receiving placebo, transfusion needs in the epoetin group were significantly reduced (25% versus 40%). In addition, patients receiving epoetin showed significantly higher energy levels, daily activity and overall QoL, while fatigue-related symptoms were reduced (Figure 3).

These data are in accordance with results seen in two large open-label non-randomised studies enrolling ~4300 cancer patients with different tumour types under myelosuppressive chemotherapy. While patients in the study reported by Glaspy et al. [43] received 150 IU/kg epoetin alfa three times per week for 16 weeks, Demetri et al. [44] used a dose of 10 000 IU with the same schedule. Both studies showed a rise in the average Hb level of ~2 g/dl at the end of treatment, resulting in a reduction in the number of transfusions of ~50% [43] and 80% [44], respectively. Improvement of QoL parameters in both studies corresponded to the increase in Hb levels (P <0.001). Demetri et al. also showed that the improvement in QoL was independent of therapy success. Using a once-weekly dosing of 40 000 IU epoetin alfa, another open-label study by Gabriole et al. [45] comprising 3012 patients showed comparable results regarding Hb increase, transfusion need and QoL.

However, although several trials indicated a significant increase in the overall QoL, a systematic review on the effectiveness of erythropoietin with regard to QoL questioned the validity and reliability of the data reported in the literature [46]. One major limitation described is the lack of masked testing of patients. Other flaws presented included lack of definition of QoL and adequate power calculations, as well as incomplete reports on methods for handling of missing data. These findings have been supported by two systematic reviews published in 2001 [47] and 2004 [48].

**Darbepoetin alfa**

Data on the use of darbepoetin alfa in the oncological setting are more scarce than for the other erythropoietins. This is due to the fact that so far most trials are dose-finding studies, investigating the efficacy and safety of different regimens used. A dose-finding study on the weekly administration of darbepoetin alfa in patients with solid tumours receiving chemotherapy indicated that the most efficient weekly dose is 4.5 µg/kg [49]. Compared with the recommended dose of 2.25 µg/kg per week after 12 weeks of therapy, this dose resulted in an earlier onset of response (7 versus 10 weeks) as well as higher response rates (76% versus 52%) and a more rapid increase of Hb levels (2.7 versus 1.5 g/dl). The same study showed that administration of 9 µg/kg every 2 weeks is comparable in efficacy to 4.5 µg/kg per week.

In most phase III studies using darbepoetin alfa, a starting dose of 2.25 µg/kg per week was used. One example is the application trial for patients with solid tumours, enrolling 320 patients with lung cancer who had Hb levels ≤11 g/dl [50]. Patients received either darbepoetin alfa or placebo for a period of 12 weeks during platinum-containing chemotherapy. In addition to a significant reduction in the proportion of patients transfused during weeks 5–12 (27% versus 52%), patients under darbepoetin alfa had a higher haematopoietic response (66% versus 24%) defined as an increase in Hb level of ≥2 g/dl or achieving a Hb level of 12 g/dl. Fifty-one percent of the patients (n = 80) showed an increase in Hb of ≥2 g/dl. Improvement in fatigue symptoms (FACT-Fatigue) was better in the darbepoetin alfa arm (56% versus 44%), but did not quite reach statistical significance (P = 0.052). This might in part be due to the delayed increase in the average Hb level after 4 and after 12 weeks, respectively (Figure 4) [51]. A dose escalation to 4.5 µg per week was applied in 43% of patients.

A recent phase III study by Hedenus et al. [52] in patients with lymphoma and myeloma gave clearer, better results. Randomised 1:1, patients with an Hb level <11 g/dl received...
Loading-dose concepts

After dose-finding studies suggested that an initially higher dose of erythropoietin might accelerate Hb increase and improve the haematological response, loading-dose concepts were evaluated. This concept could be of special relevance in the oncological setting, where treatment duration is usually limited to a few months.

A recently published study by Glaspy et al. [54] including 127 patients with solid tumours compared three different doses of darbepoetin alfa with epoetin alfa per week. Patients in the three darbepoetin groups (Hb ≤11 g/dl) received a loading dose of 4.5 µg/kg per week until a Hb value of 12 g/dl was achieved (group 1) or for 4 weeks (groups 2 and 3). Treatment was continued until week 12 with a maintenance dose of 1.5 µg/kg per week (group 1), or for 8 weeks with doses of 2.25 µg/kg per week (group 2) and 3 µg/kg every 2 weeks (group 3). Patients in the epoetin arm received 40 000 IU epoetin alfa per week, with a dose escalation to 60 000 IU after 6 weeks in non-responders.

Although initially equal doses of darbepoetin alfa were administered, the average increase in Hb values differed in the three groups (0.53, 0.70 and 0.90 g/dl). This was also the case after 12 weeks, where the Hb increases of 1.35, 1.35 and 1.28 g/dl did not reach the 8-week benchmark of ~2 g/dl. Response rates ranged between 58% and 65% (ΔHb ≥2 g/dl). The median time to response in groups 1 and 2 was shorter than in group 3 (50 versus 78 days), suggesting a faster onset of action. The investigators observed an improvement of fatigue symptoms in all three groups but did not provide data to show significance.

Similar loading-dose trials were also performed using epoetin alfa. In a study by Cortesi et al. [55], 19 patients with solid tumours and an initial Hb level <9 g/dl received a total of five injections of 40 000 IU epoetin alfa on days 1, 4, 7, 10 and 13 of chemotherapy (group A). They were compared with a historical group of 19 patients, who received 10 000 IU epoetin alfa three times per week without dose escalation for their entire treatment time of 45 days (group B). While the mean increase in Hb at day 15 was 1.7 g/dl for group A versus 0.4 g/dl in group B (P = 0.0042), average ΔHb values of 2.9 versus 0.8 were observed at day 45 (Figure 5). Response rates (ΔHb ≥2) at day 15 and day 45 were 37% and 84% in group A versus 16% and 21% in the control group, resulting in a lower transfusion rate and a better performance score for patients in the front-loading group.
Another pilot study by Patton et al. [56] in cancer patients (n = 20; Hb ≤11 g/dl) receiving chemo- or radiotherapy combined a loading dose of 60 000 IU epoetin alfa per week given for 8 weeks with a maintenance dose of 120 000 IU administered every 3 weeks. The maintenance dose was only applied in case the AΔHb after 8 weeks of therapy was ≥2 g/dl. If Hb increased >1.3 g/dl in a 2-week period of either the initial or the maintenance therapy, epoetin alfa was decreased to 40 000 IU per week. If the Hb increased to >15 g/dl, epoetin alfa was held until Hb decreased to 13 g/dl and then resumed at a dose of 20 000 IU per week. Total treatment time was 24 weeks. The median increase in Hb was 1.1 g/dl (week 4), 2.8 g/dl (week 8) and 3 g/dl at final measurement. While in seven patients the epoetin alfa dose had to be reduced to 40 000 IU per week, 13 patients were enrolled in the maintenance phase. Starting with an average Hb of 13.1 g/dl at week 9, this patients had an average Hb of 13.3 g/dl after 24 weeks.

Although larger, randomised trials are still needed, the results from these studies suggest that loading-dose concepts with a less frequent maintenance regimen might allow for a more rapid increase of Hb levels in anaemic cancer patients.

Predicting and optimising erythropoietin treatment

Since not every patient responds to rHuEPO, it has been essential to identify parameters that predict whether a patient will benefit from erythropoietin therapy. The following criteria have been found valuable in patients with cancer- or chemotherapy-associated anaemia [57–59]:

1. **Hb level of <10.5 g/dl**
2. **Low endogenous erythropoietin level (<100 mU/ml)**
3. **Appropriate stem cell reserve**
4. **Anaemic symptoms although Hb level is ≥10.5 g/dl**
5. **Low Hb level (10–12 g/dl) before chemotherapy starts**
6. **Significant drop in Hb (1–2 g/dl) until the second chemotherapy cycle**
7. **Radiation therapy, especially in patients with head and neck tumours**

In patients with a serum erythropoietin level of <100 mU/ml, a rise in Hb of >0.5 g/dl in the first 2 weeks of chemotherapy has been found to be a valuable early indicator for response to epoetin treatment (95% accuracy). Vice versa, an increase of <0.5 g/dl after 2 weeks in patients with a serum erythropoietin level of >100 mU/ml predicts lack of response with 93% accuracy [57]. Other predicting factors for response are an increase in the number of reticulocytes to more than 40 000/µl and a higher concentration in soluble transferrin receptors (>25%).

Serum ferritin levels of <100 µg/l and a transferrin saturation of >20% before the start of epoetin treatment might impair efficacy. In those patients a daily iron substitution of 100–300 mg is recommended. Owing to the elevation in iron metabolism, the prophylactic application of iron might also be advisable. Another factor that might blunt response to erythropoietin is low serum folate, which therefore should be measured initially [59].

Pharmacoeconomics

These data are also relevant in relation to cost effectiveness analyses. A recent study comparing epoetin alfa 40 000 U once weekly and darbepoetin alfa 2.25 µg/kg once weekly in patients with lung cancer suggested that epoetin alfa might be more effective and less costly compared with darbepoetin alfa [60]. Besides the drug costs, also physician fees, transfusions, laboratory tests and patient opportunity costs were taken into account. While the estimated total cost over 12 weeks was $9483 (year 2002) for epoetin alfa, the cost for darbepoetin treatment were $13 086. Costs per cumulative change in Hb were $4802 for epoetin alfa and $15 480 for darbepoetin alfa. Similarly, a randomised controlled trial in patients with lymphoid malignancies demonstrated that epoetin beta 30 000 U once weekly is as effective as epoetin beta 10 000 three times per week [61]. The reduction of the weekly dosage from 40 000 to 30 000 U offers an opportunity to further reduce the drug costs for erythropoetins. However, a randomised controlled trial showing the equivalence of epoetin alfa once weekly 30 000 U compared with 10 000 U three times per week is warranted.

Pure red cell aplasia

Pure red cell aplasia (PRCA) is a rare form of anaemia, characterised by a rapid decrease in Hb of nearly 1 g/dl per week. PRCA patients show a depletion of erythropoietic precursor cells in their bone marrow and a reduction in numbers of reticulocytes in the peripheral blood to <10 000/µl. The disease might be congenital or can be induced by various factors including infections, malignancies, thymoma, lymphoproliferative disorders, systemic autoimmune diseases and a number of drugs including insulin or interferons.

Until 1998 there were only a few single reports on PRCA. French investigators identified 13 chronic dialysis patients who developed severe transfusion-dependent anaemia between 1998...
and 2000 after treatment with epoetin for 3–67 months [62]. It could be shown that these patients had developed antibodies against epoetin, which also cross-reacted with the native hormone, thus inhibiting erythropoiesis.

Between January 1998 and April 2004 worldwide 180 cases of PRCA with anti-erythropoietin antibodies were reported in patients with chronic renal failure (CRF) treated with epoetin alfa, and 11 cases with epoetin beta. However, after procedures were adopted to ensure appropriate storage and handling, the incidence of PRCA in CRF patients decreased [63]. No further cases of PRCA in patients suffering from CRF have been reported in Europe since January 2003. No cases of PRCA have been reported so far in oncology. This might be due to the fact that the immune system of cancer patients is more disturbed by the disease or suppressed by cytotoxic therapy. In addition, compared with patients with CRF, erythropoietin therapy in cancer patients is much shorter.

**Influence of erythropoietin therapy on survival**

Pre- or peritherapeutic Hb levels of >12 g/dl have been demonstrated as independent factors for superior relapse-free and overall survival in patients suffering from cervical carcinoma, prostate cancer, bladder cancer, head and neck tumours, lung cancer, lymphoma, and myeloma [64]. One possible explanation for this phenomenon might be the improved oxygenation of tumour tissue at higher Hb levels, rendering tumour cells more sensitive to radiation and most cytostatic drugs. Another possibility is the effect of higher Hb levels on well-being and general performance of these patients [65], resulting in better compliance and the chance of conducting cytostatic treatment without delay or dose reductions.

Some studies suggest that the prophylactic use of erythropoietin in cancer patients may improve prognosis. In the Littlewood et al. study [39], the median survival in the epoetin alfa group was 17 months, compared with 11 months for patients receiving placebo, hence this was not statistically significant (P = 0.13). As this study was not designed with survival as an end point, this result must be interpreted with care. Properly designed randomised controlled trials are necessary to test the hypothesis of whether erythropoietin may indeed improve overall survival.

Casas et al. [66] reported effects of erythropoietin on the prognosis of 51 patients with small-cell and non-small-cell lung cancer stage IIIA/B. After initial cisplatin therapy, patients with Hb level <11 g/dl received epoetin alfa (150 IU/kg three times per week) concurrent with the ongoing radiochemotherapy. While 33.8% of the patients with an increase in Hb levels during radiochemotherapy reached 2-year survival, this was only the case for 1.5% of the patients with stable or decreasing Hb levels. Patients with an increase in Hb also had a significant improvement in their Karnofsky index (P = 0.001).

A recently closed trial by Blohmer et al. [67] investigated the impact of epoetin alfa in patients with high-risk carcinoma of the uterine cervix (n = 257) treated with sequential chemoradiotherapy. The first interim report might indicate an improve-ment in relapse-free survival for patients treated with epoetin alfa (10 000 IU three times per week) (17% versus 25%). Again, this observation is statistically not significant (P = 0.058; Figure 6) and these studies are not sufficiently powered to detect meaningful differences.

**Correction of Hb levels beyond anaemia**

Owing to the clinical studies suggesting higher response rates and a possibly increased overall survival in patients treated with erythropoietin, studies to correct Hb levels beyond the status of anaemia were developed. However, two recent reports, including a study in head and neck cancer [68] and one in metastatic breast cancer [69], indicated that these concepts might be associated with a higher risk of thrombovascular events and a worse tumour control. In the study published by Henke et al. [68], 351 patients undergoing radiotherapy for head and neck cancer were randomised between epoetin beta and placebo given in parallel to radiotherapy (Figure 6). The primary end point was local progression-free survival, with target Hb <14 g/dl in women and <15 g/dl in men. At baseline patients in the erythropoietin group had a relatively high median Hb level of 11.7 g/dl (range 8.5–14.4). Patients received placebo or epoetin beta 300 IU/kg three times per week, which is twice the standard dose. The mean Hb reached after 9 weeks of treatment was 15.4 g/dl (SD 1.7 g/dl). There were more episodes of hypertension, haemorrhage, thrombosis and pulmonary embolism in patients receiving epoetin beta compared with placebo (11% versus 5%). In addition, there were more patients dying of cardiac disorders in the epoetin beta group (5.5% versus 3%). The rate of locoregional tumour progression was also higher in patients receiving erythropoietin, with a relative risk of 1.69 (P = 0.007). Although there were a number of methodological concerns including imbalances in patient characteristics, higher iron supplementation in patients receiving erythropoietin and better than expected results in placebo-treated subgroups of patients, some causes of death still remained unclear despite intensive re-evaluation.

The second study recently published included 939 women with first-line metastatic breast cancer (BEST) who were prospectively randomised in a multinational multicentre study to receive epoetin alfa or placebo [69]. This study was terminated prematurely by an independent data monitoring committee.
based on first 4 months' safety data. There was a small but significant survival difference between patients receiving epoetin alfa (70%) and those in the placebo group (76%) at 12 months. This difference was due to an increased mortality in the first 4 months (41 versus 16). In particular, there was a higher incidence of fatal thrombotic and cardiovascular events (2.3% with erythropoietin versus 0.4% with placebo). The number of deaths related to disease progression in the epoetin alfa arm, however, were smaller than originally attributed by the investigators. In addition, there was a convergence of survival curves at 19 months. Although there were considerable imbalances between groups and methodological flaws, this study also suggests a higher risk of thromboembolic events in patients with higher Hb levels.

Apart from methodological limitations, the results of the studies published by Henke and Leyland-Jones may partly be explained by the increased incidence of thromboembolic complications. Interestingly, studies evaluating erythropoietin to maintain different hematocrit levels in end-stage renal failure patients and pronounced cardiovascular risk factors, showed that there is an increased mortality due to thrombovascular and cardiac events in those patients with higher hematocrit levels [70]. In patients with malignant diseases, which are often associated with an increased risk for thromboembolic complications, this concern might be even more important [71].

The reduced tumour control claimed in the studies published by Henke [68] and Leyland-Jones [69] raised additional pathophysiological discussion concerning the potential for erythropoietin to promote tumour growth. As preclinical studies reported high levels of erythropoietin and erythropoietin receptors in breast cancer cells and other malignancies, both endogenously and exogenously administered erythropoietin could theoretically promote the proliferation and survival of erythropoietin receptor expressing cancer cells [72–75]. However, these preclinical might have no or very little clinical relevance until proven otherwise.

Taken together, these studies raised concern about the safety of erythropoietins, particularly in clinical trials aimed at correcting the Hb beyond anaemic levels. These questions were discussed during a comprehensive FDA hearing on 4 May 2004 (http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2.htm). At that meeting three company-sponsored meta-analyses focusing on safety and survival of patients treated with erythropoietins were presented (http://www.fdaadvisorycommittee.com/FDC/AdvisoryCommittee/Committees/Oncologic+Drugs/050404_Aranesp/050505_AranespR.htm). The discussion highlighted the difference between studies performed according to the current ASCO/ASH guidelines [9] and those aimed beyond correction of anaemia. Clinical studies aimed at maintaining a higher Hb level such as those published by Henke [68] and Leyland-Jones [69] indicated a higher risk of thromboembolic events. As a consequence, three other studies with similar concepts were closed prematurely.

The Oncologic Drugs Advisory Committee concluded that the data available at that time were insufficient to clarify the influence of erythropoietins on tumour growth and survival. However, they did not apply restrictions on the adequate use of erythropoietin and highlighted the need for further research to clarify these questions. Important questions in future studies will focus on possible mechanism involved and on the impact of the additional iron supplementation in erythropoietin-treated patients. Iron itself may be associated with detrimental coronary outcomes [76, 77] and increase the risk of infection [78] and tumour progression [79]. In the meantime it is recommended to use erythropoietins only according to evidence-based guidelines and according to the indications granted by the regulatory agencies. Outside these indications erythropoietins should be considered only under monitored conditions in well designed controlled clinical trials.

Systematic review on erythropoietin in patients with malignancies

Bohllius et al. [80] conducted the largest meta-analysis available so far on the impact of erythropoietin in patients with malignancies. This analysis included 27 prospectively randomised controlled trials with 3287 patients. Full text and abstracts that were published between 1985 and May 2002 were included into this analysis. In particular, none of these trials was aimed beyond the correction of anaemia. All authors from the included studies were contacted for additional information with a data questionnaire. The use of erythropoietin significantly reduced the relative risk of RBC transfusion (relative risk 0.67). Although the relative risk reduction was significant for all three groups, it was more pronounced for patients with solid tumours than for patients with haematological malignancies or myelodysplastic syndrome. On average, patients in the erythropoietin group received one unit of blood less than the control group. Haematological responses were more often observed in patients receiving erythropoietin compared with patients in the control group [relative risk 3.60; 95% confidence interval (CI) 3.07–4.23]. As far as overall survival is concerned, 19 studies including 2865 randomised patients were analysed. The pooled hazard ratio was 0.81 (95% CI 0.67–0.99), suggesting that erythropoietin significantly improves overall survival in cancer patients. However, if the unadjusted data were analysed by the more conservative log-rank test, the pooled hazard ratio changes and is not statistically significant (hazard ratio 0.84; 95% CI 0.69–1.02). Since only studies published before May 2002 were included in this analysis, the trials published by Henke [68] and Leyland-Jones [69] were not included in this meta-analysis. Side-effects including thrombotic events, hypertension, haemorrhage/thrombocytopenia, rash, irritation, pruritus and seizures were also analysed. Based on the data available for this analysis, there were no statistically significant increased relative risks of suffering from any of these side-effects.

Evidence-based guidelines for erythropoietin treatment

To address uncertainties regarding erythropoietin indications and efficacy, ASCO and the ASH have developed evidence-based
clinical practice guidelines for the use of epoetin in cancer patients [9]. The guidelines are based on the results of trials published between 1985 and 1999. The ASCO/ASH guideline recommend the use of erythropoietin for patients with chemotherapy-associated anaemia with a Hb concentration of ≤10 g/dl (level of evidence and grade of recommendation: IIB). Patients with Hb levels declining to <12 g/dl might also receive epoetin depending on the clinical circumstances. In both clinical settings, RBC transfusions are also a therapeutic option depending on clinical conditions (level of evidence and grade of recommendation: IIC). Hb levels can be raised to a concentration of 12 g/dl, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dl. In the absence of direct comparisons at that time, this recommendation was based on indirect evidence and grade of recommendation: IIC).

RBC transfusion is also an option depending upon the severity of anaemia or the clinical circumstances (level of evidence and grade of recommendation: IIB). Patients with Hb levels declining to <12 g/dl might also receive epoetin when the level falls to near 10 g/dl (level of evidence: not applicable, expert opinion based on indirect evidence and biologic inference; the recommendation is based on a panel consensus).

The recommendations are based on evidence from trials in which epoetin was administered three times per week subcutaneously. The recommended starting dose therefore is 150 IU/kg three times per week for a minimum of 4 weeks, with consideration given for dose escalation to 300 IU/kg three times per week for an additional 4–8 weeks in those who do not respond to the initial dose. An alternative weekly dosing regimen (40 000 IU) can also be considered (level of evidence and grade of recommendation: IIB).

(4) Continuing epoetin treatment beyond 6–8 weeks in the absence of response (e.g. <1–2 g/dl rise in Hb), does not appear beneficial. In case iron deficiency can be ruled out, epoetin therapy should be discontinued (level of evidence: not applicable, expert opinion based on indirect evidence and biologic inference; the recommendation is based on a panel consensus).

(5) Hb levels can be raised to a concentration of 12 g/dl at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dl (level of evidence: not applicable, expert opinion based on indirect evidence and biologic inference; the recommendation is based on a panel consensus).

(6) Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximising symptomatic improvement for patients and determining the reason for failure to respond adequately to epoetin (level of evidence: not applicable, expert opinion based on indirect evidence and biologic inference; the recommendation is based on a panel consensus).

(7) Treatment with epoetin for myeloma, non-Hodgkin’s lymphoma or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anaemia should follow the recommendations outlined above (level of evidence and grade of recommendation: IIB).

(8) If in those patients a rise in Hb cannot be achieved after treatment with chemotherapy and/or corticosteroids epoetin should be used in accordance with the criteria outlined (level of evidence and grade of recommendation: IVB).

Table 5. European Organisation for Research and Treatment of Cancer guidelines for the use of erythropoietin proteins in patients with cancer

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 (grade A).

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 (grade B).

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) (grade D).

For anaemic patients who are transfusion-dependent, erythropoietic proteins should be initiated in addition to RBC transfusions (grade D).

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 (grade B).

Elderly patients experience the same benefits from treatment with erythropoietic proteins as younger patients (grade B).

The target Hb concentration should be 120–130 g/l (grade B).

The two major goals of erythropoietic protein therapy should be to improve QoL and prevent transfusions (grade A).

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 (grade A). Further studies are needed.

Within reasonable limits of body weight, fixed doses of erythropoietic proteins should be used (grade B).

We recommend the dosing of erythropoietic proteins according to Figure 1. However, the decision to dose-escalate cannot be generally recommended and must be individualised (grade B). 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 (grade D).

Despite the common use of epoetin alfa once per week (40 000 IU), there is limited evidence to support this dosing schedule (grade C). The once per week application of epoetin beta (30 000 IU) has been shown to be effective in patients with non-myeloid haematological malignancies (grade B). The once per week administration of darbepoetin alfa (2.25 μg/kg) can be recommended (grade A). There is currently limited evidence to support the use of darbepoetin alfa in every 2, 3 or 4 weeks dosing intervals (grade C).

The use of higher initial doses of erythropoietic proteins can currently not be recommended as a standard approach with epoetin alfa (grade D) or epoetin beta (grade D), but limited evidence exists for darbepoetin alfa (grade B). 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 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 (grade B).

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 (grade B).

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 (grade B).

The fear of PRCA should not lead to erythropoietic proteins being withheld in patients with cancer (grade A).

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 (grade B).

Hb, haemoglobin; RBC, red blood cell; QoL, quality of life; EPO, erythropoietin; PRCA, pure red cell aplasia.
comparisons and biological considerations. More detailed recommendations are given in Table 4. In addition, newer guidelines published by the EORTC more precisely specify the use and dose of the different erythropoietins available (Table 5) [10].

Conclusions

Anaemia, caused by the tumour itself or by cytotoxic treatment, is frequently observed in cancer patients, negatively influencing their overall QoL and also worsening prognosis. With the development of rHuEPOs, well-tolerated alternative to RBC transfusions have now become available. Treatment with epoetins has been shown to be effective in reducing transfusion rates. There is some evidence for epoetins improving QoL. A large systematic review analysing data published before 2002 hints towards a possible influence of epoetins on survival.

In order to improve efficacy and convenience of erythropoietin treatment, a number of different administration regimens are currently being tested, ranging from less frequent application of higher doses to loading-dose and early intervention concepts. Although initial promising results have been observed, the value of these concepts still has to be shown in larger randomised trials. Comparing the efficacy of the different epoetins is difficult due to a lack of large randomised head-to-head studies; so far, the three erythropoietins available have to be regarded as one class of drugs. Costs for erythropoietin treatment can be lowered if predictive factors for response are implemented and followed. In management of anemic patients, physicians should follow closely the ASCO/ASH guidelines. Clinical trials with erythropoietins aimed at correction of Hb levels beyond anaemia indicated a higher risk of thrombovascular events. Thus, treatment of patients beyond anaemia has to be regarded as experimental, and should only be conducted within clinical trials. Larger meta-analyses are needed to fully elucidate the impact of erythropoietin dosing and Hb levels on outcome.

References

31. Österborg A, Boogaerts MA, Cimino R et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple


