Management of anaemia in patients with breast cancer: role of epoetin

R. C. Leonard1*, M. Untch2 & F. Von Koch2

1South West Wales Cancer Institute, Singleton Hospital, Swansea, UK; 2Ludwig Maximilians Universität München, Department of Obstetrics and Gynecology, München, Germany

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Many patients with breast cancer suffer from anaemia, as a consequence of the disease itself or its treatment. Anaemia has a negative impact on treatment outcome and overall survival, and affects the quality of life (QoL) of patients with cancer. Previously, cancer-related anaemia was treated with blood transfusion, but this is inconvenient, offers only temporary improvement in haemoglobin (Hb) level and is associated with several risks. Consequently, blood transfusion is usually reserved for patients with severe anaemia (Hb levels <8 g/dl). Recombinant human erythropoietin (epoetin) is an effective and convenient treatment for cancer-related anaemia without the risks associated with red blood cell transfusion. Epoetin therapy effectively increases Hb levels, thereby reducing the need for emergency blood transfusion and improving the QoL of patients with anaemia and breast cancer. Epoetin beta is also effective for the prevention of anaemia and reduction of transfusion requirements in patients with a high risk of developing anaemia during chemotherapy. With the increased use of dose-intensified chemotherapy in an attempt to improve response rates, administration of epoetin to prevent anaemia could potentially benefit many patients with breast cancer.

Key words: anaemia, anaemia prevention, breast cancer, dose-dense chemotherapy, erythropoietin

Introduction

Anaemia is a common complication in patients with cancer. A variety of factors are known to be involved in anaemia development, and these relate directly to the tumour itself (blood loss, bone marrow infiltration or nutritional deficiencies) or to anticancer treatment. A comprehensive review [1] of chemotherapy trials in patients with major non-myeloid malignancies confirmed a high incidence of anaemia associated with the most common single and combination chemotherapy regimens. Depending on the malignancy and type of chemotherapy employed, up to 100% of patients developed mild or moderate anaemia [haemoglobin (Hb)<11 g/dl] and up to 80% of patients developed severe or life-threatening anaemia (Hb≤7.9 g/dl). Moreover, the prevalence of anaemia has been shown to increase during successive cycles of chemotherapy in patients with solid or haematological malignancies [2].

The consequences of anaemia in patients with cancer are often underappreciated. Anaemia results in a variety of manifestations, with fatigue being the most debilitating. Patients consider that fatigue affects their daily life more than other cancer-associated complications, including nausea and pain [3–5]. Other manifestations of anaemia include dyspnoea, cardiovascular complications, dizziness, headache, chest pain, decreased motivation, depression and anorexia [6]. Consequently, anaemia affects patients’ quality of life (QoL), and it has been shown that health-related QoL correlates directly with the severity of anaemia [7]. Anaemia is also associated with reduced tumour control and overall survival of patients with cancer [8]. Therefore, the ability to identify the patients most at risk of developing anaemia early in treatment would allow early intervention to prevent or reduce the incidence of anaemia.

Anaemia in patients with breast cancer

Breast cancer is one of the most common cancers worldwide and frequently occurs during the prime of life. Approximately 30% of patients treated with curative intent will develop a local recurrence and/or distant metastases. A patient with relapsed breast cancer can live with the disease for many years; therefore, it is important to maintain a good QoL, allowing patients to continue to work and enjoy an active life.

Adjuvant endocrine and/or combination chemotherapy remain the mainstay of systemic treatment for patients with early-stage breast cancer; [9]. Anaemia is a common occurrence in patients with breast cancer; its prevalence depending on the extent of the disease and type and duration of...
anticancer therapy [10, 11]. The most commonly used chemotherapy regimens in the adjuvant setting, FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and CMF (cyclophosphamide, methotrexate, 5-fluorouracil), induce similar rates of anaemia (Hb <12 g/dl) of 43–47% [12]. Moreover, severe anaemia (grade 3–4: Hb level ≤7.9 g/dl) has been observed in 11% of patients treated with FAC [13]. The taxanes also induce high rates of anaemia, with grade 1–2 anaemia (Hb level 10.9–8 g/dl) occurring in 67–97% of previously untreated patients receiving taxanes as single agents [1, 12]. Anaemia is also common in patients receiving radiotherapy [14]. However, anaemia occurs less frequently with the newer agents found to be effective in metastatic breast cancer, such as capecitabine and trastuzumab [15–17].

The incidence of anaemia was determined in a prospective survey of 247 Austrian patients with primary non-metastatic breast cancer receiving four cycles of adjuvant, non-platinum-based chemotherapy [18]. At baseline (after surgery), 29% of patients were found to have anaemia (Hb <12 g/dl), and another 42% of the patients developed anaemia during adjuvant chemotherapy. On multivariate analysis, the only significant predictive factor for developing anaemia during chemotherapy was the Hb level at baseline. Of particular note, only 27 of the 145 patients (19%) found to have anaemia at some point during the survey received any treatment for this condition. The findings of this study were remarkably similar to a Europe-wide survey, which included over 3000 patients with breast cancer [19]. Overall, 62% of breast cancer patients were found to have anaemia at some point during the survey, but only 26% of these received any treatment for anaemia [19]. These findings highlight the high incidence of anaemia in patients with breast cancer receiving adjuvant therapy. However, the small proportion of patients receiving treatment suggests that anaemia is frequently unrecognised and/or its importance underappreciated.

Impact of anaemia on survival in patients with breast cancer

There is compelling evidence that anaemia is associated with poor outcome in patients with breast cancer. Bottini et al. [20] used a cut-off of 13 g/dl to discriminate between normal and low Hb levels in a study of patients with operable breast cancer receiving primary chemotherapy. They showed that patients with low initial Hb levels had a lower response rate (59%) than patients with higher initial Hb levels (81%) (P<0.003). Hb level is also a prognostic factor for relapse-free and overall survival of patients with breast cancer [21, 22]. A retrospective analysis of a large trial of premenopausal patients with breast cancer [23] indicated that patients who developed anaemia (Hb <12 g/dl) during adjuvant chemotherapy were at significantly higher risk of local relapse than non-anaemic patients [21]. Hb level was also found to correlate with disease-free survival in patients with early breast cancer treated with breast conserving surgery and radiotherapy [24].

Finally, pretreatment Hb level (≥12 g/dl) was an important prognostic factor for overall survival in a study of patients with metastatic breast cancer receiving first-line paclitaxel chemotherapy (relative risk of death in patients with Hb levels <12 g/dl was 2.26 compared with patients with higher Hb) [25].

There are several possibilities to explain why low Hb levels are associated with impaired survival. First, the presence of anaemia may merely reflect the state of advancement of the cancer, with its impact on the general health of the patient reflected in anaemia and probably other co-morbid markers such as hypoalbuminaemia. Secondly, the development of anaemia may delay administration of potentially curative anticancer treatment and, therefore, affect treatment outcome. Thirdly, an indirect effect of anaemia on patient QoL and well-being may influence survival. Perhaps most importantly, however, many anticancer agents, including those commonly used in breast cancer such as radiotherapy, doxorubicin and 5-fluorouracil, require adequate tissue oxygenation in order to be effective [26]. This suggests that poorly oxygenated or hypoxic tumours will respond less well to treatment than those with better oxygen delivery.

Anaemia is a causative factor in the development of tumour hypoxia, and almost 60% of patients with locally advanced breast cancer have hypoxic tumours [27]. As well as potentially reducing response to chemotherapy, hypoxia gives rise to a more aggressive tumour phenotype and increased likelihood of distant metastases [28]. A study of patients with head and neck cancer undergoing radiotherapy has confirmed that patients with hypoxic tumours have decreased locoregional control, disease-free and overall survival rates than patients with well-oxygenated tumours [29].

Since anaemia is associated with poor outcome in patients with breast cancer, effective treatment of anaemia should be considered within the management strategy of these patients.

Treatment of chemotherapy-induced anaemia

In the past, blood transfusions were the mainstay of anaemia treatment. In an audit of blood transfusion use in patients with cancer in the UK, 19% of all breast cancer patients required blood transfusions at some time during their treatment [30]. However, this figure increased to 44% in patients with metastatic breast cancer.

Blood transfusions are inconvenient, produce only a temporary rise in Hb and are associated with several risks, including transfusion-mediated immunomodulation, haemolytic reactions, iron overload and the possibility of infection transmission [31]. Transfusions have also been associated with an increase in cancer recurrence rates [32] and a reduction in overall survival time [33]. Blood supplies are becoming a limited resource in many countries [34]. For these reasons, blood transfusion is often delayed until a patient becomes severely anaemic (Hb levels of 7–8 g/dl) [2]. Thus, patients with less severe anaemia remained untreated despite the presence of anaemia-related symptoms and their detrimental effect on QoL.
The introduction of recombinant human erythropoietin (epoetin) has provided an effective and convenient treatment of anaemia without the risks of blood transfusion. A number of studies have confirmed that epoetin results in increased Hb levels, reducing transfusion requirements and improving QoL in patients with chemotherapy-associated anaemia and solid or haematological malignancies [35–40].

The benefits of epoetin therapy have been shown both in patients with early-stage and with metastatic breast cancer. A study by Olsson et al. [41] investigated the effect of epoetin beta on the QoL of 180 patients with stage IV metastatic breast cancer and Hb levels <11 g/dl. The majority of patients were receiving second- or third-line chemotherapy. Epoetin beta significantly improved Hb levels and 83% of patients had a clinically significant response to treatment (defined in this study as an increase in Hb of at least 2 g/dl). Global QoL (Figure 1A) and the associated factors of fatigue (Figure 1B) and tiredness all improved over the course of this study, and these improvements became apparent within 4 weeks of treatment initiation. The rapid improvements in QoL represent a particularly beneficial effect of epoetin beta for the chronically ill patients included in this study, who had short expected survival times.

In a preliminary report of a controlled trial, Chang and Couture [42] also showed that epoetin could improve Hb levels, reduce transfusion requirements and improve QoL of 110 patients with breast cancer (adjuvant or metastatic). In addition, a subset analysis of patients with breast cancer included in three large, community-based trials [37, 38, 43] also showed epoetin alpha to be effective in raising and maintaining Hb levels in these patients [44]. Epoetin administration increased Hb levels, despite concomitant treatment with chemotherapy (Figure 2). Transfusion requirements for severe anaemia were significantly reduced during epoetin treatment and QoL improved significantly in association with the increase in Hb levels.

A recent study has confirmed that once weekly epoetin beta is as effective as three times weekly treatment at the same overall weekly doses in patients with lymphoid malignancies [36]. This once weekly regimen has also proved to be effective in patients with breast cancer receiving concomitant anthracycline- or taxane-based chemotherapy [45]. It is likely that the once weekly administration regimen will replace existing three times weekly regimens as it is more convenient for the patient without compromising efficacy, and is associated with reduced hospital administration costs.

**Prevention of chemotherapy-induced anaemia**

The treatment outcome of patients with breast cancer has improved with the introduction of new highly active agents. Various other strategies have been employed to improve response rates in patients with this disease. One such strategy, termed dose-dense therapy, involves intensification of therapy by shortening the interval between cycles. This strategy potentially minimises the time for tumour regrowth and may limit the development of drug resistance within the tumour, although an increase in the toxicity of the chemotherapy...
clinically significant anaemia (Hb level < 10 g/dl), whereas no accelerated chemotherapy, 52% of control patients developed a progressive anaemia (Figure 3). In addition, during the out the study (Figure 3). In contrast, control patients developed clinically significant anaemia (Hb levels < 12 g/dl) based on anaemia-related symptoms, with a target Hb level of 12–13 g/dl [50].

Studies evaluating the ability of epoetin to prevent the development of clinically significant anaemia during chemotherapy treatment of solid tumours have confirmed the feasibility of this approach. An early controlled study of 227 patients (25% of whom had breast cancer) showed that epoetin beta increased Hb levels and reduced transfusion needs of patients receiving concomitant chemotherapy [51]. In an open-label, community-based study by Hudis and Williams [52], 1632 patients with stage I–III breast cancer and Hb levels of 10–14 g/dl received epoetin alpha concurrently with anthracycline-based adjuvant chemotherapy. Hb levels improved significantly in patients with baseline Hb levels < 13 g/dl, and were maintained in patients with Hb levels > 13 g/dl. The improvements in Hb levels correlated with improvements in QoL.

Studies have also confirmed that epoetin is effective in preventing anaemia in patients receiving dose-intensified chemotherapy. One of the first studies to investigate the benefits of epoetin in supporting the administration of accelerated adjuvant chemotherapy was reported by Del Mastro et al. [53]. In this controlled study of 62 patients with early-stage breast cancer treated with six cycles of cyclophosphamide, epirubicin and 5-fluorouracil given every 2 weeks, concomitant epoetin administration maintained stable Hb levels > 12 g/dl throughout the study (Figure 3). In contrast, control patients developed a progressive anaemia (Figure 3). In addition, during the accelerated chemotherapy, 52% of control patients developed clinically significant anaemia (Hb level ≤ 10 g/dl), whereas no epoetin-treated patients developed this level of anaemia. Other studies reported in preliminary form also suggest that concurrent epoetin can maintain Hb levels and reduce the incidence of anaemia in node-positive breast cancer patients receiving dose-intensified chemotherapy [48, 54].

As part of the European Cancer Anaemia Survey, Barrett-Lee et al. [55] identified baseline characteristics that correlated significantly with anaemia development in cancer patients scheduled to receive chemotherapy. Several characteristics including baseline Hb (≤ 12.9 g/dl in women and ≤ 13.5 g/dl in men), intention-to-treat with platinum-based chemotherapy and persistent/recurrent tumours increased the risk of developing anaemia. There was an additive risk in patients with more than one of these characteristics. Assessing patients for these risk factors, particularly baseline Hb, before beginning chemotherapy for breast cancer would identify patients who are likely to become anaemic during treatment and would therefore benefit the most from early anaemia intervention [55].

Effect of epoetin on cognitive function

Long-lasting cognitive impairment is relatively common in patients with breast cancer receiving adjuvant chemotherapy [56] and is related to the intensity of treatment [57]. Preclinical studies have suggested that epoetin can cross the blood–brain barrier, where it may have marked neuroprotective activity [58]. Results from a recent study suggest that epoetin may have a role in improving the cognitive impairment associated with chemotherapy [59]. In this double-blind, placebo-controlled study of 100 patients with breast cancer, epoetin was given during four cycles of adjuvant chemotherapy. Patients receiving epoetin had significantly higher Hb levels at the end of treatment than patients receiving placebo (13.6 and 10.9 g/dl, respectively). Epoetin treatment resulted in an improvement in neurocognitive assessment test scores, whereas placebo resulted in a slight decline in scores [59]. These promising results are being investigated further.

Impact of epoetin treatment on survival of breast cancer patients

The convincing evidence that anaemia is associated with an adverse outcome in patients with cancer has prompted research on whether correction of anaemia with epoetin can improve survival rates [39, 60–62].

Erythropoietin receptors have been observed on some cancer cells [63, 64], although their functionality and clinical
relevance is currently unknown. Preclinical studies have suggested that epoetin does not induce proliferation of neoplastic cells [65]. In addition, precur- lation of various cancer cell lines with epoetin did not cause a significant change in the sensitivity to subsequent exposure to cisplatin [64].

To date, two studies have reported survival rates following epoetin treatment in patients with breast cancer [39, 62]. Littlewood et al. [39] performed a placebo-controlled trial of epoetin alpha in 375 anaemic patients with non-myeloid malignancies (30% of whom had breast cancer) and treated with non-platinum-based chemotherapy. Although the trial was not powered to evaluate survival as an end point, there was a trend towards improved survival with epoetin treatment. Median survival times were 17 months for patients treated with epoetin and 11 months for patients treated with placebo [39].

In contrast, a recent epoetin alpha trial failed to show a sur- vival benefit in patients with metastatic breast cancer receiving epoetin alpha to prevent anaemia during first-line chemotherapy [62]. At 12 months, there was a higher rate of survival in the placebo group (76%) than the epoetin alpha group (70%) (P = 0.012). This difference resulted mainly from an increase in disease progression during the first 4 months of the study in the epoetin group. Because this adverse event occurred after such a brief exposure time, it seems unlikely that it was related to epoetin administration [62]. Methodological issues have complicated interpretation of this study, with a retrospec- tive chart review suggesting more adverse prognostic factors in patients randomised to epoetin. These differences may have yielded a survival advantage for patients receiving placebo. It should be pointed out that this study was investigational in nature, using epoetin outside of its approved labelling. Also complicating interpretation of the data, a high proportion of patients in the placebo group did not become anaemic during treatment.

One other publication (although not in patients with breast cancer), also using epoetin outside of approved indications, suggests that epoetin may have a negative effect on survival when used to prevent anaemia in patients with head and neck cancer undergoing radiotherapy [61]. In contrast, a number of studies have suggested that epoetins have a beneficial effect on survival in patients with various malignancies [60, 66–68]. An independent comprehensive review including all random- ised studies evaluating epoetin to prevent or treat anaemia in patients with cancer up to the end of 2001 identified 19 studies including 2865 patients that evaluated survival as an end point [69]. Meta-analysis of these studies suggested a possible trend towards improved survival in patients receiving epoetin [hazards ratio 0.81; 95% confidence interval (CI) 0.67–0.99].

Another meta-analysis was performed using pooled data from nine randomised, controlled studies of epoetin beta only in patients with solid and haematological malignancies [70]. A total of 1409 patients (800 receiving epoetin beta and 609 receiving placebo or standard care control treatment) were included. The meta-analysis showed that no positive or negative association exists between the risk of mortality and treatment with epoetin beta (relative risk 0.97; 95% CI 0.69–1.36; log-rank, P = 0.86). The analysis showed a trend to reduced risk of tumour progression in patients treated with epoetin beta compared with control (relative risk 0.79; 95% CI 0.62–1.00; log-rank, P < 0.05). This meta-analysis confirms that epoetin beta can be safely administered to anaemic patients with solid or haematological malignancies: epoetin beta had no negative impact on overall survival and was associated with a trend towards delayed tumour progression.

Further prospective, controlled clinical trials are required to determine whether epoetin has a beneficial effect on survival of patients with cancer. A currently ongoing study, BReast Cancer–Anaemia and the Value of Erythropoietin (BRAVE), is designed to investigate the impact of epoetin beta on treat- ment outcome in patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy [45]. Recruitment of this study is now complete and its results are expected after an 18-month post-treatment follow-up.

Impact of epoetin treatment on thromboembolic events

The association between cancer and an increase in the risk of thrombosis is well documented, and is thought to be related to advancing age, surgery, decreased activity level, use of venous catheters, and therapies such as tamoxifen and chemotherapy [71]. In addition, previous thrombosis and genetic hypercoagu- gularity are strong predictors of thrombosis. In patients with renal anaemia, there is a recognised association between thrombosis and epoetin therapy, assumed to be related to a rapid rise in Hb level or polycythaemia. Isolated reports have suggested a similar association in patients with cancer [62, 72].

The incidence of thrombosis was examined in the meta-anal- ysis of pooled data from nine randomised, controlled trials of epoetin beta in patients with solid and haematological malignancies [73]. The incidence of thromboembolic events was 6% in the 800 patients treated with epoetin beta and 4% in the 609 patients treated with placebo or standard care, a difference that was not statistically significant. Importantly, the proportion of patients who died as a result of a thromboembolic event was identical for the two treatment groups (1.1% of each group). These findings are consistent with the information already contained in the product labelling for the epoetins. It is nevertheless important to avoid overtreatment as the risks of thrombosis rise with levels of Hb above the normal range.

Conclusions

Treatment of breast cancer is associated with a high rate of anaemia. Anaemia is a negative prognostic indicator for survi- val, and if left untreated, patients may require emergency blood transfusions for severe anaemia and will experience a reduced QoL. However, the impact of anaemia is frequently underappreciated and the condition often remains untreated.
Epoetin is an effective and convenient treatment for chemotherapy-associated anaemia. Several studies have shown that epoetin administered concurrently with chemotherapy can maintain Hb levels and prevent anaemia in breast cancer patients. The European Regulatory Authorities have recently recognised the benefits of the early intervention strategy and approved use of epoetin beta in patients with solid tumours receiving platinum-based chemotherapy that has a high likelihood of inducing anaemia. With the increased use of dose-intensified chemotherapy in an attempt to improve response rates, administration of epoetin to prevent anaemia could potentially benefit many patients with breast cancer.

In patients with breast cancer and anaemia, epoetin increases Hb levels; thus reducing the need for emergency blood transfusions and improving QoL. A recent study in patients with lymphoproliferative malignancies confirms that epoetin beta is equally effective when given once weekly or three times weekly. This once weekly regimen has also proved effective in patients with breast cancer.

References