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Erythropoietin Treatment in Metastatic Breast Cancer

Effects on Hb, Quality of Life and Need for Transfusion

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Erythropoietin is an effective treatment for anemia in patients with various types of cancers, but few studies have evaluated the benefit of treatment in advanced breast cancer. In this multicenter study, we investigated the influence of two different doses of epoetin-beta on the level of hemoglobin, the need for blood transfusion, quality of life and safety aspects in patients with metastatic breast cancer. A total of 180 patients were randomized to receive either 1000 IE or 5000 IE epoetin-beta subcutaneously three times per week for 24 weeks. An increase of 20 g/L was defined as a positive hemoglobin response. Blood transfusions were given, if clinically indicated. Additional laboratory values and adverse events were recorded. Quality of life was measured with the aid of the EORTC QLQ-C30 questionnaire. Hemoglobin levels increased significantly in both groups. In the high-dose group, the initial mean Hb value was 98 g/L (64–110), which increased to 121 g/L (83–165) by week 24. In the low-dose group, the mean Hb value was 99 g/L (77–110.5) and by week 24 it was 116 g/L (81–144). The majority of patients who responded to treatment did so during the first four weeks. After 4 weeks, 7 patients in the low-dose group and 24 patients in the high-dose group had increased their Hb values by more than 20 g/L. The need for transfusion was low and did not differ between the groups. Quality of life was significantly enhanced in both groups, and there was no difference in the global quality of life between the two study arms. Epoetin-beta is a well-tolerated, safe and effective treatment of anemia in patients with metastatic breast cancer. There were significant improvements in Hb levels and quality of life in both groups.

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Breast cancer is the most common form of cancer in women, with about 6000 women being given this diagnosis in Sweden each year. Roughly half of the patients are cured by primary treatment, while half suffer from local or regional relapse or from remote metastases. A patient with relapsed breast cancer may live with the disease for many years and in Sweden alone there are approximately 30000 women with active breast cancer disease. It is therefore important to ensure a high quality of life for these patients during the course of their disease, a period that can last for many years, with many patients working full time or part time during their chronic illness.

Anemia is a common symptom of the disease, and Hb levels of between 80 and 109 g/L have been reported in 55% of patients (1). This may be due to several possible causes, such as cytostatic therapy, tumor infiltration into the bone marrow, iron deficiency, secondary anemia with poor utilization of iron depots, or increased hemolysis. Depending on hemoglobin level and the treatment used, about 20% of all patients with solid tumors require transfusions, with the highest rate of 34% in patients with lung cancer (2). Some risks are associated with the transfusion of blood, however, including acute reactions of fever and chills, the risk of infection (hepatitis viruses) and, possibly, immunosuppression.

Anemia often means more to patients' quality of life than their doctors realize. An effect on the quality of life starts at an Hb level of < 120 g/L. Fatigue is an underrated symptom in patients with cancer. Fatigue, lack of enterprise, reduced appetite and low spirits can be seen even at a low degree of anemia. Many of these symptoms may be caused by the cancer, the treatment or by the anemia and it may therefore be difficult for both the patient and the doctor to recognize which symptoms arise

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specifically because of the anemia. These symptoms may be perceived as normal under the prevailing circumstances.

In this study we examined the effect of erythropoietin treatment on the quality of life of women with metastatic breast cancer. Two different dose levels were studied: 3×1000 IE $= 3000$ IE weekly (low-dose group: LD) and 3×5000 IE $= 15000$ IE weekly (high-dose group: HD). Quality of life (QoL) was chosen as the primary effect variable. Our hypothesis was that QoL increases in parallel with a rise in Hb and our aim was to investigate whether treatment with erythropoietin would lead to improved QoL in this patient group and whether there was any difference between the dose levels.

MATERIAL AND METHODS

The study comprised 180 women with metastatic breast cancer. The inclusion criteria were women over the age of 18 with metastatic breast cancer and Hb < 110 g/L for which iron deficiency anemia had been ruled out. Patients were excluded if they had uncontrolled hypertension, non-corrected iron deficiency, or a life expectancy of less than 3 months. All patients gave their informed consent. The study was approved by the regional ethics committees and the Swedish Medical Product Agency and performed according to GCP (good clinical practice). For comparison, after inclusion of the study was completed, Hb values for 43 patients with metastatic breast cancer and anemia, not treated with epoetin were registered. These patients fulfilled the same inclusion criteria and were recorded by the same study nurse.

The study design is presented in Fig. 1. The patients were randomized centrally in blocks (size 4) in a consecutive way, without any stratification for each center, to either epoetin-beta 1000 IE 3 times per week (LD group: 90 patients) or epoetin-beta 5000 IE 3 times per week (HD group: 90 patients). In the HD group, the dose was doubled if the hemoglobin increase was < 10 g/L after 4 weeks or < 20 g/L after 8 weeks of treatment.

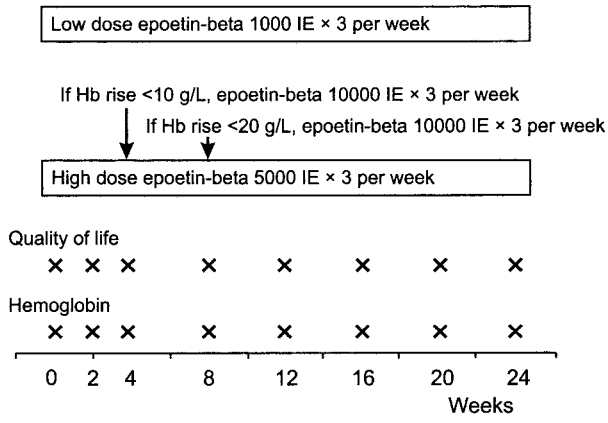

Fig. 1. Treatment schedule.

In the design of the study we discussed testing a placebo arm against a standard dose arm (Arm B), but it was considered unethical to give patients placebo and therefore a low dose was given (Arm A), with no increase in the dose of erythropoietein permitted regardless of the response. In Arm B the dose was doubled if no effect was observed.

Erythropoietin treatment was given in the form of NeoRecormon®, which was injected subcutaneously. The majority of patients were instructed on how to inject themselves. A research nurse distributed the drug and also checked how much was returned by the patient.

Oral iron supplementation with ferrosuccinate corresponding to 200 mg of iron daily was prescribed to all patients regardless of the S-ferritin value. In some cases the iron was given intravenously because of gastrointestinal side effects. If the hemoglobin exceeded 140 g/L, the epoetin-beta dose was reduced from three to two times per week. If the level exceeded 150 g/L, treatment was withdrawn until hemoglobin dropped below 140 g/L, at which time the treatment was restarted two times per week. The total treatment and follow-up period lasted for 24 weeks.

Hemoglobin: baseline hemoglobin values were defined as the average of two pre-study values, taken 2 weeks before and at randomization. Hemoglobin samples were obtained at seven time points, at weeks 2 and 4 and then every 4 weeks throughout the 24-week study period. Parallel to the analysis of Hb, the following details were registered: the need for transfusion, side effects of treatment, compliance, QoL and tumor response. The patients underwent check-ups every 4 weeks. Iron values were checked pre-study and every 8 weeks and adverse events continuously.

Quality of life

Quality of life was measured with the aid of the QLQ-C30 questionnaire. The QLQ-C30 questionnaire was developed by the European Organization for Research and Treatment of Cancer (EORTC) and has been thoroughly validated and cross-culturally tested in cancer patients (3–5).

The instrument consists of 30 items comprising 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain and nausea/vomiting); one global health status/quality of life scale, with 6 single items assessing additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation and diarrhoea) and one scale measuring financial difficulties resulting from the disease. Furthermore, a tiredness module was added. Items chosen per protocol were fatigue, physical functioning, global QoL and tiredness.

Scoring: Items are rated on 2-, 4-, or 7-step scales. All scales and single item measurements range from 0 to 100 after linear transformation. A high score on a functional scale represents good function. A high score for global

Table 1

Metastatic disease 180 patients, number of patients and percentage per group

Site of metastases	Low-dose group	High-dose group
Skeleton	89 (19%)	88 (18%)
Lung	79 (16%)	82 (17%)
Liver	80 (17%)	81 (17%)
Skin	80 (17%)	81 (17%)
Node	80 (17%)	81 (17%)
Other	73 (15%)	74 (15%)

health status/quality of life represents a high QoL, whereas a high score for a symptom or item represents severe symptoms or problems. Response was defined as an increase in QoL score of >1 and the primary efficacy variable was the proportion of patients with increased QoL per group.

Tumor treatment

A total of 141 patients underwent chemotherapy, the majority, 91 (65%), were on second or third line treatment (Table 1). The chemotherapy was mostly an anthracycline- or taxan-containing regimen. A smaller group, 34 patients, had hormonal therapy as the only treatment. They were equally distributed between the groups. Five patients had no active tumor treatment, only best supportive care, which was given to all patients.

All the patients had metastatic disease; 43 patients had only one metastatic site, 92 had two different metastatic sites and 40 had three or more metastatic sites.

Statistics

All analyses were determined in advance and performed as 'Intention to treat'.

Repeated measurements analyses were used to analyze time-dependent data, and statistical comparisons to test differences between the two groups were done using Student's t-test for uncorrelated means, after validation for normal distribution using the Shapiro Wilk test. The within-group analyses were done with the pairwise Student's t-test for correlated means. Multiple comparisons of continuous data were performed by analyses of variance. The procedure proposed by Fisher was used to control for multiplicity (6, 7).

In order to evaluate hypotheses of variables in contingency tables, the χ^2 test was used or, in the case of small, expected frequencies, Fisher's exact test. In addition, descriptive statistics and graphical methods were used to characterize the data.

In the study we used multiple hypothesis testing, where each hypothesis was analyzed separately and the existence of patterns and the consistency of the results were considered in the analyses. All analyses were carried out with the SAS system (8) and the 5, 1 and 0.1% levels of significance were considered. In the case of a statistically significant result, the probability value (p-value) was given.

RESULTS

A total of 180 patients were enrolled in the study, of which 90 patients were randomized to each of the two groups. The clinical characteristics of the two groups were comparable (Table 1). The mean age in the LD group was 58 years (range 30–82) and 57 years in the HD group (range 35–83 years).

Three patients withdrew before starting treatment with epoetin-beta; 177 patients were treated. One patient did not meet the inclusion criteria (pre-study mean Hb 110.5 g/L).

A total of 36 patients in the HD group doubled their epoetin dose to 10000 IE three times per week, because of an increase in hemoglobin level of Hb <10 g/L after 4 weeks or Hb <20 g/L after 8 weeks of treatment. Six patients in the LD group and 18 patients in the HD group decreased their epoetin-beta dose because of an Hb of >140 g/L. In the HD group, 14 patients interrupted epoetin-beta treatment because of an Hb of >150 g/L.

The change in Hb over time for all patients as well as for the groups separately is described in Fig. 2. In the LD group (receiving 3000 IE per week) the original value was 99 g/L (77 g/L–110.5 g/L), which rose during treatment and had reached Hb 116 g/L (81 g/L–144 g/L) by week 24. The corresponding levels in the HD group (receiving 15000 IE per week) were Hb 98 g/L (64 g/L–110 g/L) at the start and Hb 121 g/L (83 g/L–165 g/L) by week 24. Significant differences were observed between the groups at weeks 8, 12, 16 and 20, but not at week 24. For comparison, Hb values for 43 patients with metastatic mammary carcinoma not treated with epoetin were registered. These patients fulfilled the same inclusion criteria and were recorded by the same study nurse. In this group the Hb value was stable throughout the observation period.

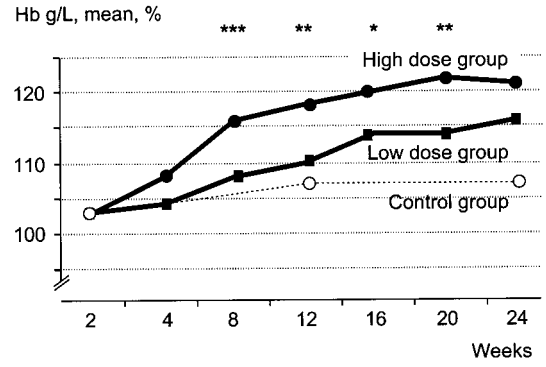

Fig. 2. Hb values in relation to epo dose and time. Significant differences between the treated groups are observed. Week 8: $p<0.006$ (***); week 12: $p<0.02$ (**); week 16: $p<0.05$ (*) and week 20: $p<0.02$ (**). Control group patients ($n=43$) collected after the trial were not treated with erythropoietin.

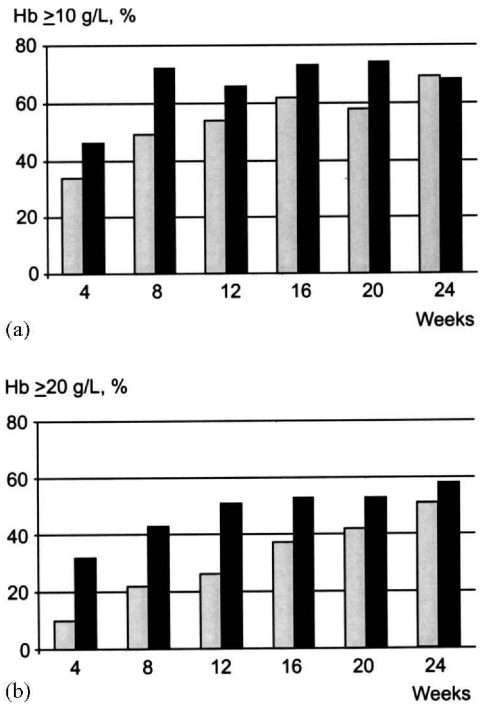

Fig. 3. (a) Percentage of patients with increased Hb ≥ 10 g/L. Statistically significant differences between groups at week 8: $p < 0.004$ and week 20: $p < 0.05$. (b) Percentage of patients with increased Hb ≥ 20 g/L. Statistically significant differences between groups at week 4: $p < 0.001$; week 8: $p < 0.006$ and week 12: $p < 0.03$. □ Low-dose group; ■ high-dose group.

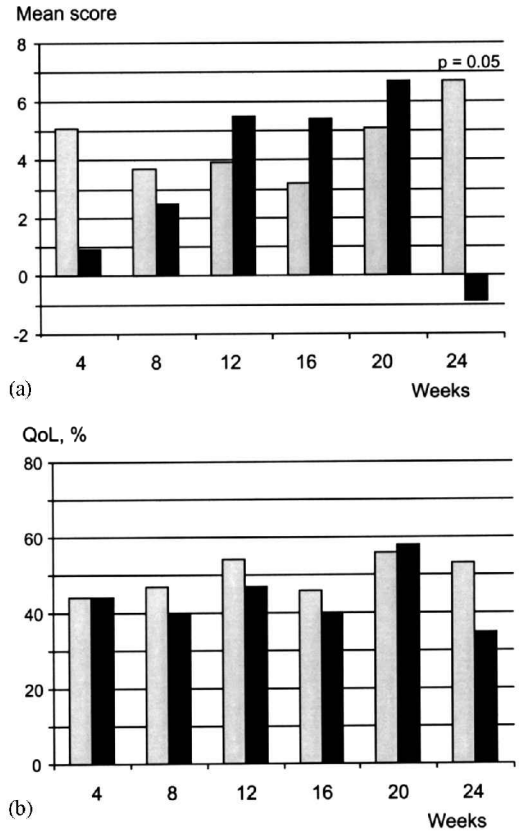

Fig. 4. (a) Changes in mean scores for global quality of life. (b) Percentage of patients with increased global quality of life. □ Low-dose group; ■ high-dose group.

The number of patients in which Hb increased by more than 10 g/L and by more than 20 g/L in the LD and HD groups is shown in Fig. 3a and b. Response to treatment normally occurred within the first four weeks. The mean time for an increase in Hb showed no significant difference between the groups.

Responses in relation to initial values are plotted in Table 2. Here we see that the majority of patients who responded have initial values of Hb ≥ 90 g/L. With an initial value of Hb < 80 g/L none of the patients responded.

Quality of life

A baseline QoL assessment was completed in 172/180 patients. Follow-up assessments at 4, 8, 12, 16, 20 and 24 weeks were carried out for 143, 138, 119, 119, 109 and 109 patients, respectively. The change in QoL variables from baseline to follow-up was calculated for each of these subgroups of patients.

The mean scores for changes in global QoL are shown in Fig. 4a. During the study period there were no significant differences between the treatment groups with regard to global QoL ratings. Within the LD group, however,

Table 2

Hb response in relation to initial Hb values

Baseline Hbg/L	Low-dose group			High-dose group		
	n	≥10 g/L	≥20 g/L	n	≥10 g/L	≥20 g/L
<80	3	–	–	2	–	–
80–90	11	4	2	15	8	5
90–100	34	13	6	28	12	7
>100	43	16	9	44	22	18

Table 3

The effect of global quality of life in relation to initial Hb-values. Actual p-values

	Low-dose group							High-dose group						
	n	Weeks						n	Weeks					
		4	8	12	16	20	24		4	8	12	16	20	24
>100 g/L	43	–	–	–	0.04	0.04	0.02	44	0.01	0.04	0.03	0.02	–	–
90–100 g/L	34	–	–	–	–	–	–	28	–	0.05	–	–	–	–
<90 g/L	13	–	–	–	–	–	–	18	–	–	–	–	–	–

there was a significant increase in global QoL at week 24 ($p < 0.05$). The percentage of patients per group with increased global QoL is presented in Fig. 4b. In Table 3 the effects of QoL are checked in relation to initial Hb-values. The significant effects in global QoL are seen almost exclusively in the patient group with initial Hb-values ≥ 100 g/L.

Physical functioning improved in both groups throughout the study period, although no significant increase was seen in either of the groups. The percentage of patients with improved physical function was about 25–30% in both groups.

Fatigue

In Fig. 5a–c we show the impact of the treatment on fatigue over the study period. There was a significant decrease in fatigue in the HD group during the period from week 8 to week 20 (Fig. 5a). A statistically significant decrease in the fatigue score in the HD group could be detected after 4 weeks ($p < 0.04$), 8 weeks ($p < 0.01$), 12 weeks ($p < 0.0001$), 16 weeks ($p < 0.03$) and 20 weeks ($p < 0.008$). There was no significant difference between the groups. The proportion of patients with decreased fatigue was higher in the HD group than in the LD group during the entire study period. This difference was most marked from the middle of the period (week 12) with a statistically significant difference between the groups at week 20, (40% of the patients in the LD group and 63% in the HD group) ($p < 0.05$)/($p < 0.02$). Within the LD group, fatigue was reduced during the whole study period, but not to the same extent as in the HD group. In Fig. 5b the percentage of patients with less fatigue than before treatment is presented. From these graphs, it is clear that the effect is better in the HD group than in the LD group and there is a significant difference between the groups by week 20. It can also be seen that fatigue is reduced for all patients at all time points by 30–60%. In Fig. 5c we have registered the percentage of patients with unchanged or less fatigue. From this figure it can be seen that the majority of patients fall within this definition.

Tiredness (Fig. 6a–b) was significantly reduced in the HD group in the middle of the period ($p < 0.005$). For the whole study period, tiredness was reduced in both dose groups and an average of over 40% of patients reported less tiredness during the whole study period.

Scores for dyspnea, nausea/vomiting, sleep disturbances and financial problems were low throughout the study period and no significant changes in QoL were seen, but there was a strong trend towards a reduction of dyspnea in the LD group at week 4 ($p < 0.05$) and in the HD group at week 20 ($p < 0.06$).

The need for transfusion

There was no difference between the groups regarding the need for transfusion. In the 12 weeks prior to the study, 23 patients (25%) in each group had received blood transfusions. During the course of the 24-week study, 32 patients (36%) in the LD group and 30 (34%) in the HD group received blood transfusions.

Compliance

A total of 109 patients completed the study period, while 71 withdrew before the study period ended: 38 (42%) in the LD group and 33 (37%) in the HD group.

There were no significant differences between the groups regarding the reason for withdrawal. The most common causes were tumor progression and death (40 patients: LD 21 patients; HD 19 patients). Thirteen patients withdrew because of an unsatisfactory effect of treatment, 7 patients (LD 4; HD 3) withdrew for personal reasons and 5 patients (LD 2; HD 3) withdrew because of adverse events. On the whole, the medication was well tolerated.

DISCUSSION

In breast cancer, an incidence of 55% has been reported for anemia, defined as Hb levels of 80–109 g/L (1). In our sample group, anemia was defined as an Hb of < 110 g/L in a homogeneous patient group consisting of women with metastatic breast cancer in whom iron deficiency anemia had been ruled out. The increase in Hb over time for the two groups is presented in Fig. 2 and shows how patients in both groups responded to the treatment, with the curves running largely parallel. Of course, there is the question of what happens to the patients' Hb values when no epoetin is given. Therefore, when inclusion of the study was completed, we continued to follow patients who met the crite-

ria for the study and measured the Hb values, without any epoetin, and treated them with our standard regimens. So far, 43 patients have been collected. For these patients with metastatic mammary carcinoma and anemia, but not treated with epoetin, the Hb values remained stable throughout the observation period (Fig. 2).

Although the increase in Hb was greater in the HD group and also occurred faster, a clear effect was seen also in the LD group. There was no difference between the groups in the need for transfusion. The response to the treatment was seen within the first two to four weeks in the majority of patients. It has previously been reported that most patients who respond to treatment show an increase in Hb levels within 6 weeks, although a few patients do not respond before 8–16 weeks (9). The number of patients who responded with an increase in Hb of 10 g/L is essentially the same in both groups, but for increases of 20 g/L a clear difference could be observed in favor of the HD group. The patient groups are well balanced for age and location of metastases and therefore comparable.

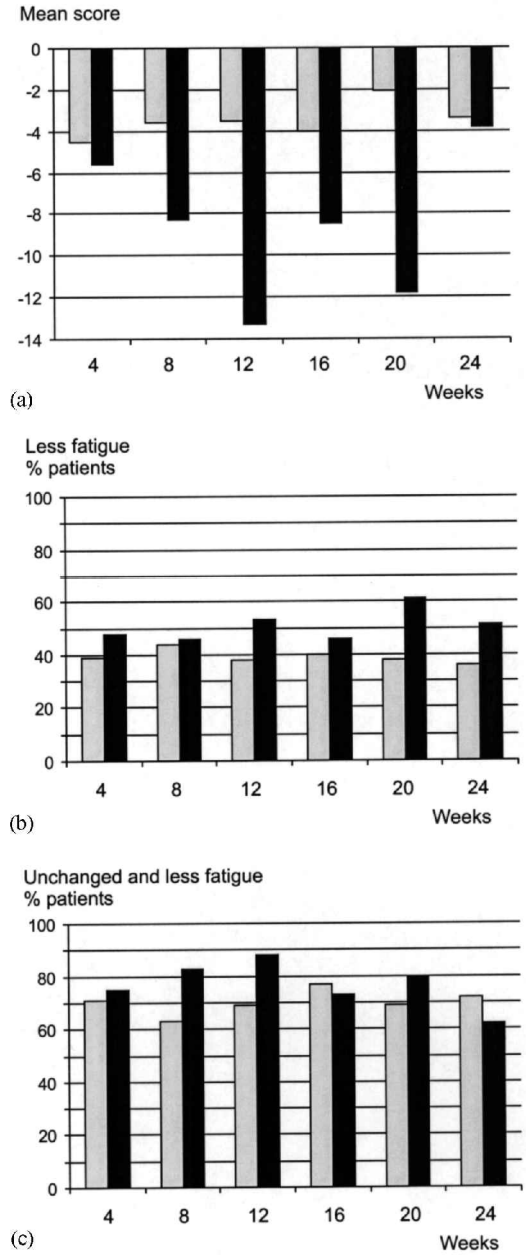

Fig. 5. (a) Less fatigue, mean score changes. (b) Percentage of patients with less fatigue. (c) Percentage of patients with unchanged or less fatigue. □ Low-dose group; ■ high-dose group.

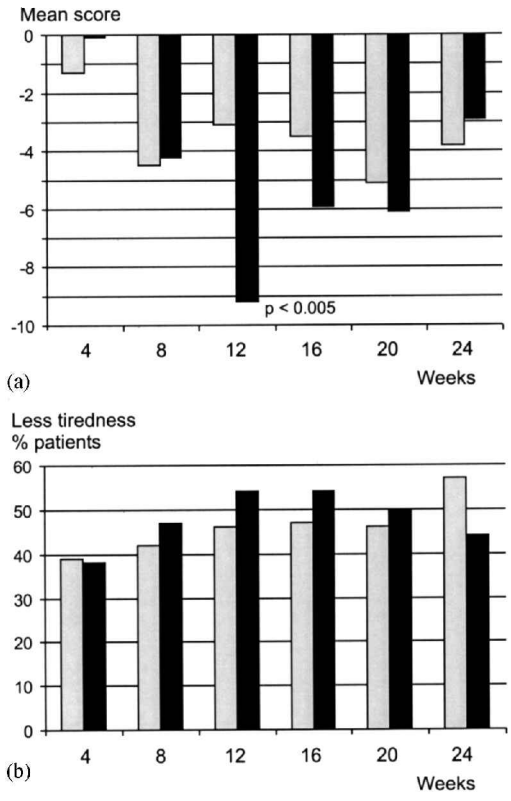

Fig. 6. (a) Mean score changes for patients with less tiredness. (b) Percentage of patients with less tiredness. □ Low-dose group; ■ high-dose group.

In previous studies it has been reported that about 60% of patients with anemia in cancer respond to epoetin treatment (10). The response frequency is the same with or without simultaneous chemotherapy. If a response is defined as an increase in Hb of >10 g/L, 89% of the patients in the LD group and 87% in the HD group responded during the first 12 weeks. Comparable results for an increase in Hb of >20 g/L are 61% and 83%, respectively. This suggests that patients with anemia and metastatic breast cancer are an appropriate group for treatment with erythropoietin. However, the optimal dose for these patients is still questionable. Unfortunately, one cannot predict which patient is likely to respond to erythropoietin treatment. It is known, however, that a very high endogenous s-epo level reduces the chance of responding (11), as does a demonstrated large need for blood transfusion (12). Other factors impeding any response to

treatment are ongoing infection and other active inflammatory bowel disease. However, the vast majority of patients with rheumatoid arthritis and inflammatory bowel disease do respond to epoetin treatment (13, 14).

All patients received iron supplementation orally or intravenously, although iron-deficiency anemia was an exclusion criterion. The reason for this was that functional iron deficiency is a known feature in the anemia of cancer and inflammatory bowel disease. The efficacy of epo treatment is optimized if iron supplementation is given simultaneously (15).

The patients were well motivated for their treatment and the majority learned how to administer the injections themselves without difficulty. The dropouts that did occur were mainly due to tumor progression and the death of the patient. The patients were all in stage IV breast cancer, but were still able to benefit from the treatment, giving an increase in QoL in both groups. Other studies have also reported that patients with other advanced tumor diseases can benefit from erythropoietin treatment. Metastatic breast cancer can be a slow disease with very gradual tumor progression, and in such cases progressive anemia often arises. The median survival time for patients with metastatic disease treated with conventional chemotherapy doses and regimens is 12 to 24 months (16). If blood transfusions are chosen as treatment, these treatments may be needed for a long period of time. This leads to difficulties for the patient in being tied to the hospital, as well as the risk of autoantibodies, allergic reactions and blood-transmitted infectious diseases. The patient may also feel worse if the Hb level is allowed to fluctuate violently. With erythropoietin treatment, a smooth and steady increase in the level of Hb can be achieved, which may be more physiologically favorable for the patient. The patients also experienced an improvement in their QoL. It is feasible and conceptually desirable to use QoL measures in most supportive care studies (17). Indeed, QoL may be the most appropriate endpoint since the maintenance of an acceptable QoL is the most important primary goal in chronically ill, incurable patients. In this trial we found a significantly increased global QoL in both of the erythropoietin dose groups. Moreover, fatigue decreased significantly during the course of the study. Three-quarters of cancer patients experience fatigue, and fatigue is the most frequent complaint among these patients (18). No specific mechanism, similar to the induction of anorexia by the tumor necrosis factor, has been shown for fatigue. The etiology is probably multifactorial, with anemia playing an important role, but other factors such as the stress induced by surgery, chemotherapy, infections, weight loss and depression may also cause fatigue. The most pronounced effects on fatigue occurred in the HD group.

Many studies have shown that treatment of anemia with erythropoietin has a positive effect on QoL (19–23).

In several previous studies it has also been shown that an increase in QoL is achieved with an increase in Hb of > 20 g/L (24–26). In this study, an increase in QoL was observed in both the HD and the LD groups, but a greater percentage of patients increased their Hb level by > 20 g/L in the HD group. However, the increase was statistically significant in both groups. Moderate doses seem to be satisfactory for a distinctly improved QoL.

A potential weakness of the present study was the large number of patient withdrawals, mainly due to general deterioration or death. However, it can nevertheless be concluded that even a small improvement in Hb may lead to improvement in QoL in patients with advanced progressive mammary carcinoma.

A large proportion of patients reported improvement from randomization to the first assessment. This demonstrates the rapid effect of the erythropoietin treatment on the QoL variables, which is important for patients with a short, expected survival time.

Social function scoring improved at weeks 4 and 16 in the LD group. These patients were given subcutaneous injections three times a week. The majority learned how to administer the injections themselves and they often established frequent and close contacts with the nurse at the clinic who taught them the technique. In some cases there was also intensified contact with the community nurse/health visitor. It is possible that this phenomenon is also reflected in this effect variable.

Emotional function scores were also significantly improved at weeks 8 and 16 in the HD group. Many patients who receive treatment that increases their contact with the health service often find this to be positive. They have direct contact with the nurse and doctor in charge in a way that would not otherwise be possible. Many patients testify to feeling that they are noticed, that they are important, extra carefully controlled, and that current symptoms are interpreted, assessed and dealt with somewhat more explicitly than usual. Moreover, for some older patients who have problems with loneliness, increased contact with the health service can fulfill a social function. In addition, if one feels better, this effect becomes even more obvious.

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