# Treatment of associated anemia in different hematological disorders with epoetin alpha

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The communication is summarizing results of study aimed to ascertain the efficacy of treatment with epoetin alpha in patients with different hematological disorders and, at the same time to evaluate the impact of this treatment on quality of their lives. Treatment efficacy in separate patients of the monitored population has been evaluated not only according to hemoglobin level increase, but also according to its effect on erythrocyte products consumption needed to control anemic syndrome. Overall 134 patients with different lymphoproliferative disorders were included in the evaluation. Full-extended monitoring, i.e. at least 3-month treatment with epoetin alpha, was passed by 127 (94.8%) patients. Favorable effect of epoetin alpha administration was most often reported in patients with multiple myeloma (85.7%), Waldenström's macroglobulinemia (80%) and chronic lymphatic leukemia (76.7%). Conversely the lowest efficacy was reported in the group of patients with myelodysplastic syndrome. Administration of epoetin alpha within treatment of underlying anemia in numerous hematological disorders represents suitable alternative to the substitution therapy via erythrocyte transfusions. Approximately 75% of monitored patients showed improvement of life quality, in some cases irrespective of results of treatment of their underlying disorder.

*Key words: anemia, treatment, erythropoietin, quality of life*

Anemia is a common accompanying symptom of an array of hematological disorders. The causes are usually complex. The main pathogenous mechanism is the mechanical oppression of normal hematopoesis by infiltrative growth of tumor cells into the bone marrow. Other contributive factors may also include cytokine production, possible renal insufficiency, blood loss, hemodialysis, administration of chemotherapy or radiotherapy and last but not least recurrent infectious diseases due to the secondary immunodeficiency, etc. [21, 22]. Anemia could be one of the reasons for the deteriorating quality of life in patients with neoplastic disease [5], therefore actions aimed at its prevention should become an integral part of scheduled therapeutic regimens [12, 24]. The goal of treatment of patients with neoplastic disease should not be limited to just maximizing the therapeutical effect, but also to maintain acceptable quality of life [7].

The administration of recombinant erythropoietin [14, 15] in patients with anemia caused by various hematological malignancies became a modern therapeutic approach of the last decade. The gene for erythropoietin was first cloned by Amgen Company in 1983 and first studies of its clinical efficacy were published as soon as in late 80's [8, 19]. Transfusion therapy is still predominant clinical approach in patients with anemia. Despite permanently increasing quality of individual transfusion products, this therapy is still associated with possible adverse effects. At the same time, multiple studies have shown that in some patients with hematological malignancies, erythropoietin administration results in pronounced increase of hemoglobin levels or at least in decreased erythrocyte transfusion requirements.

Our study was aimed to ascertain the efficacy of treatment with epoetin alpha in patients with various hematological disorders and at the same time to evaluate the impact of this treatment on quality of their lives.

## Patients and methods

The total of 134 patients (67 men and 67 women) with hematological malignancies from 21 hematological facilities within Czech Republic participated in the study between January 2000 and March 2002. Hemoglobin values of 100 g/l and less prior to therapy or the requirement of administration of at least 2 blood transfusions within the last 2 months to correct anemia either with or without the therapy of primary disorder were the main selection criteria. The minimum period of erythropoietin administration required for the evaluation of its possible efficacy was set to 3 months.

The elimination of other possible causes of anemia, i.e. blood loss, hemolysis, folic acid and vitamin B12 deficiency, was required for participation in the study. Other exclusion criteria included uncontrolled hypertension, severe thrombocytopenia, renal insufficiency, epilepsy and history of allergic reaction to the tested preparation. Acceptable levels of blood transferrin saturation had to be ascertained in patients with demonstrated iron defficiency prior to their participation. Transferrin saturation levels were subsequently monitored monthly in all patients. Aside from transferrin saturation levels, body weight, blood pressure, heart rate, hemoglobin values, hematocrit, leukocyte and thrombocyte counts, ferritin and creatinine levels were compulsorily evaluated in all patients on a monthly basis. In addition, the following characteristics were recommended for evaluation: reticulocyte counts, levels of urea, aminotransferases and endogenous erythropoietin. Apart from the blood count dynamics, the application of blood transfusions was recorded in order to assess therapy effectiveness.

Therapeutic regimen consisted of subcutaneous administration of epoetin alpha (EPREX, Janssen-Cilag) 3 times per week. The initial dose was set, according to manufacturer's recommendation, to 150 IU/kg of patient weight. Results of subsequent evaluation of therapy effect were grounds for possible increase of dosage. On the contrary, should the monthly increase of hemoglobin concentration exceed 20 g/l, the dosage was reduced. Administration of erythropoietin was terminated upon reaching hemoglobin endpoint values of 120 g/l. Erythrocyte transfusion was recommended in cases where hemoglobin values decreased under 85 g/l or when symptoms of anemic syndrome appeared.

Within the scope of this study, possible changes in the quality of life during the erythropoietin therapy were assessed by the simplified version of FACT (the Functional Assessment of Cancer Therapy scale) questionnaire using a point scale (0 – no problems, 100 – extremely strong manifestation). In order to evaluate therapy effects, two forms were filled, one prior to the commencement of the study and the other after 3 months therapy. Following characteristics were assessed on the point scale: tiredness and weakness during mild and strong exertion, during the common activities and at rest, dyspnea, sleep disorders, loss of concentration, sexual disorders, job limitations, and limitations in activities of daily living.

The basic assessment of patient numbers in individual groups was performed by summary statistics based on binary and ordinary variables. The assessment of absolute values of epoetin dose, vital signs and biochemical test results was performed by t-test and Mann-Whitney test. The assessment of relative probability of number of transfusion and parameters of quality of life was performed by binomial test, contingency tables analysis and Fisher's exact test.

## Results

Evaluation was made in 127 patients (94.8% of initial number of participants), 65 women (51.2%) and 62 men (48.8%), i.e. in those who passed through the minimum of 3 months of epoetin alpha therapy. Sixty patients (47.3%) were undergoing chemotherapy during the course of epoetin administration, 39 patients (30.7%) were treated by chemotherapy in the past and the remaining 28 patients (22.0%) were not treated either by chemotherapy or radiotherapy so far. The reasons for exclusion of 7 subjects were as follows: 3 died of the primary malignancy (2 of multiple myeloma and 1 of chronic lymphatic leukemia), 2 showed possible adverse reactions to Eprex and 2 were excluded for diagnostic uncertainty. Basic characteristics of the evaluated group are shown in Table 1.

**Table 1. Selection of participating patients**

| Diagnosis | Number | Average age (years) | Median of age (years) | Standard deviation (years) |
|---|---|---|---|---|
| MM | 34 | 69.6 | 70 | 9.26 |
| CLL | 34 | 67.9 | 71 | 10.58 |
| MDS | 29 | 65.8 | 70 | 15.13 |
| NHL | 9 | 55.1 | 53 | 9.25 |
| WM | 6 | 71.5 | 73 | 10.99 |
| Other | 15 | 49.7 | 52 | 20.73 |

MM – multiple myeloma, CLL – chronic lymphocytic leukemia, MDS – myelodysplastic syndrome, NHL – non-Hodgkin lymphoma, WM – Waldenstrom's macroglobulinemia.

The average single dose of erythropoietin throughout the period of evaluation was 130.77 IU/kg of patient weight. The comparison of average monthly dosages showed no statistically significant difference between 1st and 2nd month of administration (increase of 5.92 IU/kg of patient weight). Statistically significant difference has been firstly shown when comparing the average monthly dosages of erythropoietin administered during the 3rd with the do-

sages administered during the 1st month (decrease by 15.41 IU/kg, p=0.004) and the 2nd month of evaluation (decrease by 21.33 IU/kg, p<0.001). Two patients exhibited symptoms of possible adverse reactions during the course of erythropoietin. The connection with epoetin was undisputable in one patient, who demonstrated burning and redness of skin at the application site. The other patient with myelodysplastic syndrome suffered from pulmonary embolism during the period of evaluation and the connection is therefore deemed possible.

Statistically significant increase of hemoglobin and hematocrit levels has been noted in most of the patients during the period of evaluation. This correlated with the statistically significant decrease in a number of patients requiring blood transfusion as well as the decrease of total blood transfusion administrations during the course of study when compared to the initial period (p<0.001). Therapeutic effect became usually evident within the first 4 weeks of administration. Otherwise, there were no statistically significant changes in any of the monitored parameters, including the levels of diastolic and systolic blood pressure. The dynamics of average hemoglobin levels and transfusion therapy requirements during individual months of assessment, as well as the results of their statistical comparison, are shown in Figures 1 and 2. The best therapeutic effect was demonstrated in patients with lymphoproliferative diseases. Statistically significant increase in hemoglobin levels and/or decrease of transfusion requirements was recorded in 85.7% of patients with multiple myeloma, in 80% of patients with Waldenstrom's macroglobulinemia, in 76.7% of patients with chronic lymphocytic leukemia, and in 63% of patients with non-Hodgkin's lymphomas. The lowest (35%), although still clinically applicable efficacy of epoietin administration was demonstrated in patients with myelodysplastic syndrome.

Our study demonstrated statistically significant improvement of life quality for all assessed parameters in 82.9% of participating subjects, independently of the diagnosis and in some cases even regardless of the outcome of the initial disorder therapy. Deterioration of life quality during the evaluation period was demonstrated in 8.6% of participating subjects. The deterioration was always clearly attributable to the progression of the primary disease. Subsequent evaluation of individual parameters of quality of life improvement was limited to patients, who successfully completed the study and exhibited improved or stable quality of life. Statistically significant improvement in tolerability of evaluated activities before and after treatment was demonstrated for tiredness and weakness during high intensity exertion (p<0.001), low intensity exertion (p<0.001), usual activities (p<0.001) and at rest (p<0.001), for dyspnea (p<0.001), loss of concentration while reading or watching TV (p=0.008) and for activities of daily living (p<0.001). There was no statistically significant improvement either

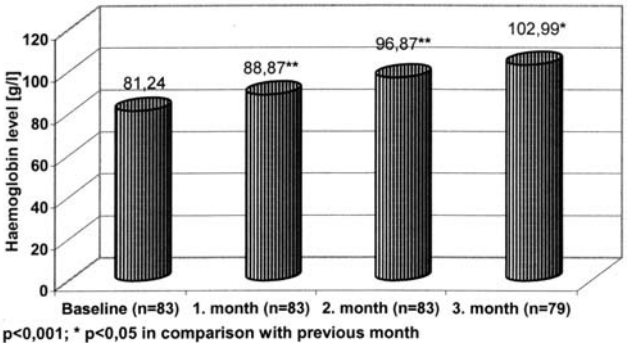



**Figure 1. The dynamics of hemoglobin levels during the evaluation period.**

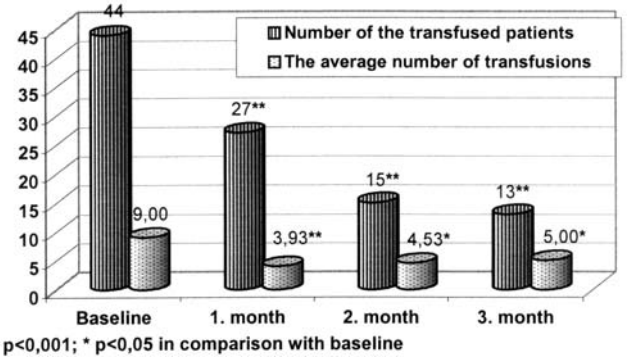



**Figure 2. The dynamics of transfusion therapy requirements during the evaluation period.**

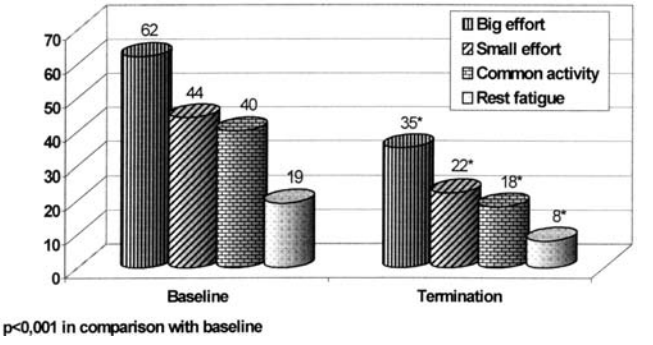
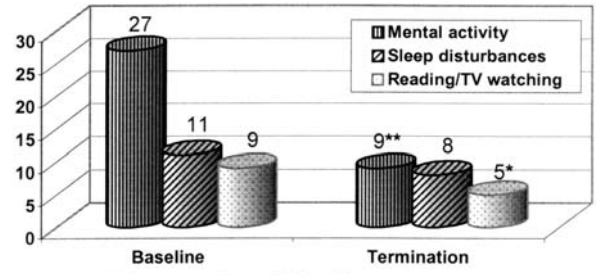


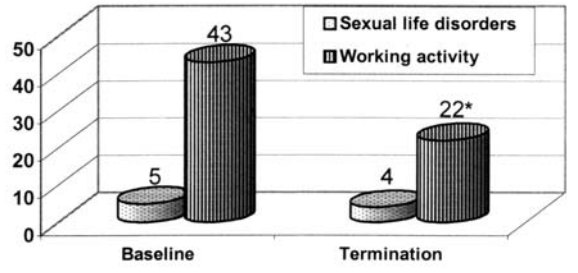

**Figure 3. Comparison of quality of life prior to and after the evaluation period (1).**

in the quality of sexual life as in the sleep disorders. For better transparency, the dynamics of individual parameters of quality of life in the group of patients is also shown in Figures 3 to 5. Statistically significant difference in hematocrit and hemoglobin levels was demonstrated in patients claiming improved or stable quality of life when comparing both the entry and final values (p<0.001) and when comparing the values recorded during subsequent follow-ups (p<0.05). No statistically significant difference for any of other evaluated parameters was shown during the course of study.




** p<0,001; * p=0,008 in comparison with baseline

**Figure 4. Comparison of quality of life prior to and after the evaluation period (2).**




* p<0,001 in comparison with baseline

**Figure 5. Comparison of quality of life prior to and after the evaluation period (3).**

## Discussion

The results of our study verified in accordance with previously published results of other studies that erythropoietin administration can control anemia in a number of patients with advanced multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) and chronic lymphatic leukemia (CLL) [1, 6, 17, 18, 26], that were originally dependent on transfusion therapy. Therapeutic effect is usually evident within one month of the start of application. Along with the rectification of hemoglobin values, patients often experienced improved quality of life, in some cases even regardless of the outcome of initial disorder treatment. This issue is currently a subject of several studies, which should resolve the dispute concerning connection between hemoglobin values and quality of life and effect of chemotherapy and radiotherapy as well.

Of all the diagnoses assessed in our study, the most pronounced effect of erythropoietin therapy was shown in the group of patients with multiple myeloma. However, the therapeutic potential in patients with other lymphoproliferative disorders was also promising. With respect to the present availability of erythropoietin in common clinical practice, this therapeutic regimen should be used preferably before the commencement of transfusion therapy of severe anemia, especially in the group of patients with malignant lymphoproliferative diseases [23, 24]. Currently performed studies will determine the optimal initial and target doses of hemoglobin during the erythropoietin therapy, primarily with respect to the patients quality of life. Possible potentiation of chemotherapy [10] is suggested based on the well known fact that the efficacy of radiotherapy is dependent on the hemoglobin level in patients with solid tumors [9, 27, 28].

Current views of the need to determine the entry values of erythropoietin are controversial [11]. Results of some studies suggest better efficacy in patients with relatively insufficient endogenous erythropoietin production [4, 20], suffering from MM, NHL and CLL. However, low entry erythropoietin level was recorded in just 75% of patients with lymphoproliferative disorders, moreover, no such connection was shown in patients with solid tumors. Recent studies disclosed other important prerequisite for erythropoietin efficacy, the sufficient reserve of normal bone marrow function, expressed by the platelet count ($100x10^9$/l).

Generally, patients quality of life is accepted as one of important criteria for the evaluation of therapy success in neoplastic disorders [5]. The results of our study verified the well known fact, that the quality of patients life is considerably dependent on hemoglobin values [2, 16]. Target levels of hemoglobin of 110–120 g/l are considered optimal. However, improvement of the quality of life is apparent even in cases, where erythropoietin therapy resulted in stabilization of the hemoglobin values, thus eliminating the need of further transfusion therapy [7]. The improvement obtained during erythropoietin therapy as opposed to transfusion therapy can certainly be related to higher values of hemoglobin reached during the treatment; the levels reached by blood transfusions are usually lower by 10–20 g/l. This is partly because of the possible complications of transfusion therapy. Despite their significantly decreasing incidence due to new procedures they still exist. In view of the above facts, the administration of artificial blood seems to be an interesting option for future.

The incidence of adverse effects during the erythropoietin therapy is rare. The most common is the clinically insignificant increased blood pressure [29] and slight increase of thrombocyte count at the onset of therapy. In the past much more serious adverse effects related to the erythropoietin administration were reported. So far there have been only dozens of cases of pure red cell aplasia based on antibody immune reaction during the course of epoetin alpha therapy [3]. This has only been limited to patients with chronic renal insufficiency so far. No such adverse reaction has been observed in patients treated with erythropoietin for malignancy associated anemia. In order to prevent this adverse reaction, it is recommended that in patients with chronic renal disease erythropoietin should be administered only intravenously. The possible enhanced risks of thromboembolic disease during erythropoietin therapy have been known for a long time, particularly in the area of sport doping, where it is used to raise the target hemoglobin values.

However, caution is also required during erythropoietin administration in patients with malignancy associated anemia. Late findings emphasize adherence to the maximum target hemoglobin values of 130 g/l, as the studies aimed at the assessment of increasing hemoglobin values on further improvement of quality of life with disclosed significantly increased risks of thromboembolic complications.

Higher cost of erythropoietin therapy when compared to blood transfusion substitution therapy is still a persistent problem. This problem is however relative, considering the fact, that in blood transfusions adverse reactions management and possibly also inferior outcomes of therapy of primary disease should have been included in the cost. The cost of blood transfusion is also escalated by the improvements in quality of transfusion products (for example technologies of leukoreduction, irradiation). On the other hand there is even room for price reduction of erythropoietin therapy. Reduction of erythropoetin dose is feasible by the consistent supplementation of iron based on regular monitoring of iron deposits. Required weakly doses of erythropoietin decreased by 30% to 70% [25] in patients with chronic renal insufficiency when the regular iron substitution was employed. Therefore this substitution should become a part of erythropoietin therapeutic regimen even in patients with malignancy associated anemia [13]. Transferrin saturation proved to be the most suitable parameter for the evaluation of iron deficiency. Iron should be supplemented when transferrin saturation drops below 25% [23]. For this reason, regular measurements of transferrin saturation were integrated in our study.

Erythropoietin administration is eligible alternative to erythrocyte transfusion substitution therapy in the treatment of anemia associated with an array of hematological diseases. Its broader application in clinical practice is prevented by higher cost of this undoubtedly safer therapeutic approach. Our study in a group of selected patients suggested that this approach should be further tested primarily in anemic patients with various lymphoproliferative disorders. Correction of anemia in these patients often leads to improved quality of life regardless of the outcome of treatment of primary disease.

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