ANALYSIS OF THE INFLUENCE OF VARIOUS FACTORS ON ANEMIA IN PATIENTS WITH LYMPHOID MALIGNANCIES

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SUMMARY – Anemia is a frequent complication of lymphoid neoplasms as a result of the disease and myelotoxic chemotherapy, and has a significant impact on treatment outcome, survival and quality of life. The aim of this study was to investigate clinical characteristics of anemia in lymphoid malignancies and to assess the need of anemia treatment in the context of modern therapeutic possibilities. Fifty-five patients (32 female and 23 male) with non-Hodgkin's lymphoma (NHL, n=30), chronic lymphocytic leukemia (CLL, n=8) and multiple myeloma (MM, n=17) were included in the study. The influence of age, sex, type of malignancy and chemotherapy on the prevalence, severity and type of anemia before and after chemotherapy was analyzed. The prevalence of anemia was 51.02% before (A1) and 55.31% after (A2) chemotherapy. Women had a higher prevalence of anemia than men (63% *vs*. 43%), but the severity was higher in men at the beginning (103 *vs*. 99 g/L Hb) and at the end of treatment (101 *vs*. 89 g/L Hb). The highest prevalence of anemia was found in MM (69%), followed by NHL (44.4%) and CLL (40%) before chemotherapy, and in MM (68.7%), CLL (42.9%) and NHL (20.8%) after chemotherapy. The prevailing anemia was anemia of chronic disease (53.8%), followed by anemia due to multiple causes (anemia of chronic disease + iron deficiency anemia or anemia of chronic disease + hemolytic anemia; 30.7%), anemia due to iron deficiency (11.5%) and hemolytic anemia (7.6%). The prevalence of anemia as a consequence of the disease is high in lymphoproliferative disease, but there was no significant rise under chemotherapy, even showing a decline in NHL patients (44% *vs*. 21%), however, the severity of anemia increased. Since stage 1 anemia according to the WHO prevailed, only a small number of patients required transfusion therapy. About 27% of all patients had hemoglobin values <100 g/L during chemotherapy and could be candidates for erythropoiesis-stimulating agent treatment.

Key words: *Anemia – treatment; Lymphoma – treatment*

Introduction

Anemia is a common diagnosis in cancer patients and depends on the type of malignant disease and type of therapy applied. The prevalence and type of anemia in cancer patients vary from disease to disease and are influenced by different factors like patient age, introduction of chemotherapy, and others. In cancer patients aged over 70, the prevalence of anemia increases to 70%-80%. According to previous investigations, the average prevalence of anemia was 40%-50% in colon cancer, 70% in ovarian cancer, and 90% after platinum-based chemotherapy. The etiology of anemia in patients with malignancies may include neoplastic cell bone marrow infiltration, particularly in hematologic malignancies, nutritional deficiencies (iron, vitamin B12 and folate), hemolysis, and treatment- or disease-induced bone marrow suppression as the most common reason[1,2].

Lymphoid malignancies have become ever more frequent among malignant diseases. The prevalence

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of anemia, according to various studies, ranges between 40% and 80%. Anemia has been incorporated in the prognostic indices for lymphoid malignancies as an independent factor of disease severity and prognosis. On the other hand, anemia is a major cause of weakness and general bad feeling. Fatigue caused by anemia is the most common and long-lasting symptom in patients with hematologic malignancies. Poor quality of life is in direct correlation with the degree of anemia in cancer patients. Improving the quality of life in cancer patients treated with chemotherapy and those with advanced disease having undergone palliative measures only has become the main goal of treating anemia in these patients. The stage and type of anemia determine therapeutic approach[1-3].

Despite the high prevalence and broad implications, the number of patients treated for anemia in hematologic malignancies remains relatively low, about 50%[4]. New treatment options include erythropoiesis-stimulating agents (ESA) and continuous erythropoietin receptor activators (CERA), which are still in the phase of research. After years of clinical experience with ESA, it is obvious that correction of anemia in patients with malignancies is possible. The latest guidelines have been designed upon these experiences and include definition, identification and optimal treatment of anemia in malignant disease. Organizations such as the European Organisation for Research and Treatment of Cancer (EORTC), the National Comprehensive Cancer Network (NCCN), the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) recommend treatment guidelines that suggest intervention with erythropoietin therapy when hemoglobin (Hb) concentration decreases below 100-110 g/L[4,5].

The aim of this study was to investigate clinical characteristics of anemia in lymphoid malignancies before and after chemotherapy administration, to assess the need of treatment of anemia and to evaluate this treatment in the context of modern possibilities available.

Patients and Methods

Fifty-five patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) not previously treated with iron, transfusion, folate or vitamin B12 were included in the study. There were 23 male patients (mean age 66 years) and 32 female patients (mean age 63 years). CLL was diagnosed in eight, MM in 17 and NHL in 30 patients. The most common chemotherapy regimens were CHOP, CVP, chlorambucil, MP, and VAD, including the new generation of chemotherapeutic agents like rituximab. The mean number of chemotherapy cycles *per* patient was 5.9.

All patients underwent the following investigations before and after chemotherapy: complete hemogram with red blood cell (RBC) indices, reticulocyte count (RTC), peripheral blood smear examination, direct Coombs test (DCT), bone marrow aspiration (only before therapy), serum iron (SI), ferritin (SF), total iron binding capacity (TIBC), percentage saturation (psat) and parameters of disease activity, i.e. C-reactive protein (CRP) and lactate dehydrogenase (LDH). Hemoglobin level below 120 g/L (normal: male 160-180 g/L and female 140-160 g/L) was taken as the limit of anemia, while the severity of anemia was classified according to the World Health Organization (WHO) scale (Table 1)[1]. Anemia was categorized as due to either anemia of chronic disease (ACD; SF >300 mcg/L); iron deficiency anemia (IDA; psat <20% and SF <100); autoimmune hemolytic anemia (AIHA; DCT positive); and anemia due to multiple causes (MA), e.g., a combination of IDA and ACD (psat <20%, SF 30-200 with TIBC <42 μmol/L).

The standard methods of descriptive statistics were used in the study. Differences between the groups were tested using Student's t-test, χ^2-test, Wilcoxon test and Kruskal-Wallis test in the Statistica 7 program.

Table 1. The World Health Organization anemia grading system

Severity according to WHO	Hemoglobin (g/L)
Grade 0	110-119
Grade 1 (mild)	95-109
Grade 2 (moderate)	80-94
Grade 3 (serious/severe)	65-79
Grade 4 (life-threatening)	<65

Table 2. Values of hemoglobin (Hb) and prevalence of anemia in patients with lymphoid malignancies before and after treatment according to sex, age and type of lymphoid neoplasm

	n	Hb1 (g/L)	A1 (%)	Hb2 (g/L)	A2 (%)	*P* (Hb1:Hb2)	*P* (A1:A2)
Sex							
Male	23	120±21.29	99.0 (42.8%)	114±29	89.0 (47.3%)	0.518	**0.003**
Female	32	113±18.6	103.0 (62.9%)	109±26.5	101.0 (58.6%)	0.4561	0.272
Total	55	116±19.9	102.0 (54%)	111±27.3	97.0 (55%)	0.3331	0.2727
Age							
≤65 yrs	22	119±23.8	96.0 (42%)	113±26.2	94.0 (58%)	**0.0007**	0.8003
>65 yrs	33	114±17.1	104.0 (62%)	112±21.2	97.0 (52%)	0.6933	0.1952
Type of malignancy							
NHL	30	121±19.7	105.0 (44%)	119±22.3	112.0 (21%)	0.3045	0.2334
MM	17	102±14.9	98.0 (69%)	102±15.39	106.0 (68.7%)	**0.0231**	0.4408
CLL	8	124±19.5	101.0 (40%)	120±28.4	99.0 (43%)	0.715	0.5176

A = Hb values and prevalence of anemia before (1) and after (2) chemotherapy; Hb = Hb values for the whole group before (1) and after (2) chemotherapy; NHL = non-Hodgkin's lymphoma; MM = multiple myeloma; CLL = chronic lymphocytic leukemia

Results

The mean hemoglobin concentration for the whole group was 116.0±19.9 g/L before (Hb1) and 111.1±27.3 g/L after (Hb2) chemotherapy cycles ($P>0.05$). There was no statistically significant difference between the hemoglobin concentrations in men (Hb1 120, Hb2 114 g/L) and women (Hb1 112, Hb2 109 g/L) (Table 2).

The difference in hemoglobin values was statistically significant according to diagnosis (NHL *vs*. MM *vs*. CLL) both before (Hb1 121 *vs*. 101 *vs*. 124 g/L; $P=0.0331$) and after chemotherapy (Hb2 119 *vs*. 102 *vs*. 120 g/L; $P=0.0029$). MM had significantly lower hemoglobin concentrations than other groups (Table 2).

The overall prevalence of anemia in lymphoid malignancies in this study was 51.02% before and 55.31% after chemotherapy ($P>0.05$). The prevalence of anemia in CLL group was 40% with Hb1 mean value of 101 g/L and 42.9% with Hb2 mean value of 99 g/L. In MM group, the prevalence was 69.1% with mean Hb1 of 98 g/L and 68.7% with mean Hb2 106 g/L. The prevalence of anemia in NHL group was 44.4% with mean Hb1 105 g/L and 20.8% with mean Hb2 value 112 g/L (Table 2).

The prevalence of anemia in men was 43% with mean Hb1 99 g/L and 47% with mean Hb2 89.2 g/L ($P=0.0003$). In women, the prevalence of anemia was 62.9% with mean Hb1 103 g/L and 58.6% with mean Hb2 101 g/L ($P>0.05$) (Table 2).

The grade and severity of anemia according to the WHO scale according to age, sex and diagnosis are shown in Table 3. It is obvious that there was no significant increase in the overall prevalence of anemia after chemotherapy related to diagnosis, however, the severity of anemia showed an increase.

ACD was the most common type of anemia (53.8%, 14/26 patients), MA was present in 30.7%, IDA in 11.5% and AIHA in 7.6% of all patients. There were no statistically significant differences before and after chemotherapy in other variables (RTC, SI, TIBC, SF, CRP and LDH) tested in this study, but they had a tendency to improve. Also, the value of LDH in NHL group was significantly lower after chemotherapy ($P=0.0345$).

Discussion

The type of tumor disease and treatment option (chemotherapy and/or radiotherapy) have a significant impact on hemogram and the occurrence of anemia. The severity of anemia at diagnosis is a sign of the disease severity and has an unfavorable effect on

Table 3. Prevalence of different stages of anemia according to WHO scale according to sex, age and type of malignancy before and after treatment

		Before chemotherapy			After chemotherapy		
		Gr 0-1	Gr 2	Gr >=3	Gr 0-1	Gr 2	Gr >=3
Sex	n	Hb 95-120	Hb 80-95	Hb <=80	Hb 95-120	Hb 80-95	Hb <=80
Male	9	67%	33%	0%	33%	60%	7%
Female	17	54%	46%	0%	91%	9%	0%
Total	26	69%	27%	0%	62%	23%	19%
Age							
≤65 yrs	10	60%	20%	20%	50%	37%	13%
>65 yrs	18	78%	22%	0%	53%	27%	20%
Type of malignancy							
NHL	12	83%	8%	8%	50%	0%	50%
MM	11	54%	46%	0%	83%	17%	0%
KLL	3	100%	0%	0%	0%	100%	0%

NHL = non-Hodgkin's lymphoma; MM = multiple myeloma; CLL = chronic lymphocytic leukemia

patient outcome. Anemia has been taken in various models to predict outcome in patients with hematologic neoplasms like multiple myeloma, Hodgkin's lymphoma, NHL and CLL. Anemia was included in the prognostic index of multiple myeloma by Durie and Salmon, where the hemoglobin level <85 g/L was associated with greater tumor mass and poor survival. In Hodgkin's lymphoma, anemia with hemoglobin level <105 g/L is one of the most powerful predictors of poor outcome. Anemia has long been recognized as an important prognostic factor of indolent and aggressive lymphoma. Anemia did not become part of the International Prognostic Index (IPI) because it was not tested when the index was developed. Including hemoglobin less than 120 in IPI significantly increases the index accuracy to predict survival and detect treatment failure. After introducing IPI in clinical practice, a prognostic index for follicular lymphoma (FLIPI) was developed taking hemoglobin level lower than 120 g/L. Follicular lymphoma is the most common indolent lymphoma and the second most prevalent of all lymphomas. In CLL patients, anemia is included in the Rai and Binet index and is associated with poor disease outcome[6-9]. According to the British and French authors, the incidence of anemia in patients with NHL and Hodgkin's disease at diagnosis is 30%-40% and increases to 70% after chemotherapy. In 1763 Italian cancer patients, the prevalence of anemia was 56% before and 73% after treatment. The high prevalence of anemia is associated with lymphoid malignancies, and according to various studies is 22%-82% before and 55%-88% after chemotherapy[10-12]. The results of the present study are consistent with the results reported by other authors. The mean prevalence of anemia in lymphoid malignancies was 51% before and 55% after treatment. The highest percentage of patients with anemia was in MM group. In this group, the stage of anemia was most severe because most patients had the highest grade of disease (grade 3 according to Salmon and Durie). The prevalence of anemia in CLL and NHL groups was very similar, about 40%. In this study, we found a higher prevalence of anemia in female than in male patients (63% *vs.* 43%), however, men had a higher grade of anemia than women (Hb1 99 *vs.* 103 g/L) before and after (Hb2 89 *vs.* 101 g/L) treatment.

The incidence of anemia in lymphoid malignancies investigated in this study was not significantly increased after chemotherapy, but we detected progression in the severity of anemia as a result of myelotoxicity. Even more, the overall prevalence of anemia in NHL and MM groups was slightly lower after therapy, interpreted as a good therapeutic response. Study results showed a significant LDH decrease in

NHL after treatment (as an independent factor of disease activity).

Besides the unfavorable impact on disease outcome and treatment outcome, anemia has a proven impact on the patient quality of life. It is generally considered that treatment of anemia results in better overall survival and disease-free survival, but still there are no well structured and prospective studies to prove it. According to Functional Assessment of Cancer Therapy (Anemia Scale quality of life survey), there is direct negative correlation between quality of life and severity of anemia. Improvement in the quality of life in cancer patients during chemotherapy and in those with advanced disease on palliative regimen has become the main goal of treating anemia in these patient populations[1-5]. The treatment of anemia in cancer patients depends on the cause and severity of anemia. According to the present and other studies, anemia of chronic disease (50%), anemia due to multiple causes (30%) and symptomatic treatment account for the highest percentage of anemias. Only a small percentage of cancer anemias are due to iron deficiency (in this study 11%) or hemolytic anemia (7.6%) and can be treated casually. Treatment of tumor anemia with hemoglobin values lower than 80 and clear symptoms of anemia requires RBC transfusion. Transfusion remains a treatment option depending on the severity of anemia and clinical urgency of the situation. Some investigations have shown that patients who received blood transfusions under less rigorous conditions (Hb <= 100 g/L) had a higher mortality rate than patients who received transfusions under stringent criteria (Hb <= 70g/L). Milder anemia in practice is usually not treated[13-15]. At long term, tumor anemia can be corrected by ESA (epoetin alfa, epoetin beta, epoetin gamma and darbepoetin). ESA have shown good results in long term treatment of tumor anemia, with the response rate from 28% to 80%. The need of transfusions, according to various studies, ranges from 9% to 50% of patients. ESA have been demonstrated effective in many patients with anemia in hematologic malignancies through achieving higher levels of hemoglobin and reducing the need of transfusions. The result of successful treatment of lymphoid neoplasms is close to 80%. According to the American Society of Clinical Oncology and the American Society of Hematology guidelines, it is recommended to use erythropoietin for the treatment of patients with chemotherapy induced anemia whose hemoglobin concentration is less than 100 g/L[2,3,5]. In our study, it was 26% of all patients. However, therapy with ESA has increased mortality due to the increased incidence of thromboembolic incidents, so it is not recommended to achieve hemoglobin values greater than 120 g/L. It also increases mortality due to stimulation of tumor growth, so the use of ESA products in patients with cancer is limited to the treatment of chemotherapy induced anemia only[16,17].

In conclusion, the prevalence of anemia in lymphoid malignancies is high at the disease diagnosis, especially in MM patients, but comparison with other authors did not show any significant rise in the incidence of anemia during chemotherapy. In MM and NHL patients, hemoglobin values improved by more than 100 g/L with the treatment, but worsening of the anemia was recorded in younger men. Accordingly, chemotherapy regimen in the treatment of lymphoproliferative disease mainly does not worsen anemia, and it is mostly a sign of the disease severity.

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Sažetak

ANALIZA UTJECAJA RAZLIČITIH ČIMBENIKA NA ANEMIJU U BOLESNIKA S LIMFATIČNIM NEOPLAZMAMA

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Anemije su česta komplikacija kod limfatičnih neoplazma kao rezultat bolesti i mijelotoksične kemoterapije, a imaju značajan utjecaj na ishod liječenja, preživljenje i kvalitetu života. U istraživanje je bilo uključeno ukupno 55 bolesnika (32 žene i 23 muškarca) s limfatičnim neoplazmama: 8 s kroničnom limfatičnom leukemijom (KLL), 17 s multiplim mijelomom (MM) i 30 s ne-Hodgkinovim limfomom (NHL). Analiziran je utjecaj spola, dobi i tipa malignoma na učestalost, stupanj težine i tip anemije prije i nakon provedene kemoterapije. Učestalost anemija prije kemoterapije bila je 51,02%, a nakon provedene kemoterapije 55,31%. Najveća učestalost anemije prije kemoterapije utvrđena je kod MM (69%), potom kod NHL (44,4%) te KLL skupine (40,0%) na početku terapije. Nakon kemoterapije učestalost je bila kod MM 68,7%, NHL 20,8% te KLL 42,9%. Tijekom terapije rasla je i težina anemije u odnosu na stanje prije kemoterapije. Prevladavala je anemija kronične bolesti (53,8%), zatim anemija uslijed višestrukog mehanizma nastanka (30,7%), anemija zbog deficita željeza (11,5%) i hemolitična anemija (7,6%). Kod limfatičnih neoplazma visoka je učestalost anemija kao poseljedica bolesti, a pod utjecajem kemoterapije se nije značajnije povećala. Povećala se težina anemije. Budući da je prevladavala anemija 1. stupnja prema SZO, samo manji broj bolesnika je zahtijevao transfuzijsko liječenje. Oko 26% svih bolesnika imalo je vrijednosti hemoglobina niže od 100 g/L tijekom kemoterapije i oni bi bili kandidati za liječenje sredstvom za stimuliranje eritropoeze radi poboljšanja kvalitete života.

Ključne riječi: *Anemija – liječenje; Limfomi - liječenje*