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Chemotherapy induced anemia in patients with malignant diseases: A Montenegro study

Vladimir Todorovic, Jadranka Lakicevic, Nada Cicmil Saric, Anka Popovic, Vesko Vujicic, Danko Zivkovic, Aleksandra Kovacevic, Rozalinda Isjanovska

ABSTRACT

Aims: Oncology patients treated by chemotherapy (CT) often develop different levels of anemia. We analyzed efficacy and safety of three times weekly administration of epoetin beta in hematologic and solid tumors in Montenegro. Methods: One hundred and twenty anemic patients with solid tumors (75 patients) and non-myeloid hematological malignancies (45 patients) were treated with epoetin beta in the period from January 2009 till May 2012. We analyzed efficacy in terms of hemoglobin (Hb) level, transfusion requirement, dosing schedule and safety in this open label, single arm, non-interventional study. Anemic patients with Hb level <11 g/dL, treated with chemotherapy were included in this first multicentre oncology study in Montenegro. Statistical multivariate analysis method was used. Results: In our study, most of patients had moderate anaemia, while 5.8% had severe level. Statistical significance was found in level of Hb during epoetin beta therapy compare to baseline and other study visits (p = 0.01). The percentage of patients with normal Hb values was increasing during the treatment. The need for blood transfusion was decreasing during epoetin beta therapy (first visit 8.3%, fifth visit 1.7%). Majority of patients (68%) did not report any adverse event. Two patients had thromboembolic events. Conclusion: Administration of epoetin beta 30.000 IU three times weekly significantly increased Hb levels in anemic patients with different solid tumors and non-myeloid hematological malignancies who were receiving chemotherapy. The number of required transfusion is decreasing during the study treatment. Therapy with epoetin beta was well tolerated. Benefits of using epoetin beta were confirmed in patients with chemotherapy induced anemia.

Keywords: Anemia, cancer, chemotherapy, epoetin beta, safety

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INTRODUCTION

Majority of patients on chemotherapy (CT) develop anemia during the treatment. Anemia is a negative

prognostic factor in patients with cancer. Studies showed that patients with anemia have lower tumor control and shorter disease free and overall survival after CT, compared with patients with normal hemoglobin (Hb) levels [1, 2].

The European Cancer Anemia Survey (ECAS) 2004. have shown high prevalence of anemia patients with cancer. The frequency of anemia was high in most types of malignancies (70% of patients had anemia during observational period). Several reviews of incidence of anemia showed that almost all patients developed at least mild or moderate anemia and 79% of patients developed severe anemia (Hb 8.0–10.9 g/dl) [3].

Anemia in cancer patients is associated with advanced stage of disease, older age and the duration of CT regimen [4]. Oncology patients need earlier transfusion and there is a shorter time for indication of these interventions. Several transfusions may be indicated and during CT, epoetin beta therapy may reduce the need for transfusions [5].

During cancer treatment anemia may not be recognized or may be underestimated and low percentages of patients are receiving an appropriate therapy. In ECAS survey 17% of patients received epoetin treatment.

Epoetin beta stimulates human erythroid bone marrow precursor cells and stimulates growth of erythropoiesis cells. Epoetin beta does not stimulate growth of megakaryocytes.

In everyday practice, anemia is treated most often by using transfusions of red blood cells. The benefits are: rapid increase of Hb and hematocrit level and rapid improvement in anemia - related symptoms. Transfusion of red blood cells may cause transfusion reactions, virus transmission, bacterial contamination, iron overload. Recombinant Human erythropoietin avoids all mentioned risks. Epoetin beta stimulates human erythroid bone marrow precursor cells and these results in growth of marrow cells as erythropoiesis. Epoetin beta does not stimulate megakaryocytes' differentiation. The most common side effects are hypertension and thromboembolic events [6, 7].

Meta-analysis of studies with epoetin beta evaluated the impact and initial Hb levels on overall survival, tumor progression and thromboembolic side effects. Total numbers of 2297 patients were included. There was no association between high target Hb levels and an increased risk of mortality, disease progression or thrombosis with epoetin beta compared with control group. The results showed that there is no impact on survival or tumor progression when therapy was starts at Hb levels at 11 g/dL [8].

The most frequent side effects of epoetin beta are: headache, rising of blood pressure, flu like symptoms, skin reactions as rash, increased number of platelets, thrombosis and in small number of patients hypertensive crisis.

Some studies showed that early erythropoietin intervention is beneficial with better efficacy and decreased number of transfusion indications. No increase of treatment cost was associated with early application of epoetin beta [9].

The analysis of six studies giving epoetin beta in different tumor types in more than 4200 patients showed that epoetin beta is effective and well tolerated with significant Hg increase in 4 weeks (1 g/dL) and 12 weeks (2 g/dL). The value for quality of life (QoL) improvement correlates with normalisation of Hb levels and shows the need for effective anemia management in different cancer localizations [10].

MATERIALS AND METHODS

Patients and Methods

Efficacy and safety of anemia treatment with three times weekly administration of epoetin beta in hematologic and solid tumors were analyzed. This study was conducted in three oncology centres. 120 patients were included in the period of January 2009 till May 2012. These anemic patients have solid tumors (75 patients) and non-myeloid haematological malignancies (45 patients). Our special interest was related to hemoglobin levels, indication for transfusion of red blood cells, epoetin beta dosing schedule and safety in these open label, single arm, multicentre, non-interventional study. Patients were included if they had anemia with hemoglobin level <11 g/dL and received chemotherapy. Exclusion criteria were contraindication of epoetin beta, therapy resistant hypertension and allergic reactions to active ingredients or to preserves of drug. This study is open label, prospective, non-comparative, multi-centre and observational (non-interventional). The study protocol was approved by the Central Ethical Committee of Clinical center of Montenegro for each of the three participating centers. Patients were treated in Clinic for Oncology and radiotherapy, Centre for Hematology and in Special hospital for Lung diseases in Brezovik. The treatment with epoetin beta was given according to oncology practice and product written information. Treatment with epoetin beta was monitored for four months period. After the treatment period patients were followed for two weeks more. Data collected for statistical analysis were: the type of malignant disease, levels of hemoglobin during therapy, number of transfusions applied, dosing scheme and side effects of epoetin beta. Safety report of epoetin beta was based on the number of reported adverse events, intensity of adverse events (mild, moderate, serious and life threatening), relationship of the adverse events and the study drug, frequency of serious adverse events and their outcome.

Statistical analysis

We used measures of central tendency and dispersion of data and analysis of variance (Anova) confirmed with Tukey's HSD (honestly significant difference) test used to

determine whether significant differences existed (95% confidence interval). A multivariate analysis was used to analyses all variables examined in time.

RESULTS

One hundred and twenty patients were included from January 2009 until May 2012. in three Montenegrin oncology centers. Seventy-five patients had solid tumor (lung cancer, breast cancer, colorectal cancer, gastric cancer, kidney cancer, ovarian cancer, cervical cancer, laryngeal cancer) and forty-five patients had non-myeloid hematological malignancies. Patients with allergic reaction on active ingredients, in the case of therapy resistant hypertension and if therapy is contraindicated, were not enrolled. The number of female patients was slightly higher and the median age was 59 years (Table 1).

According to hemoglobin level on basic study visit 113 patients had moderate anemia, (Hb 8 –10.9 g/dL), 7 patients (5.8%) had severe anemia with Hb level lower than 8 g/dL. At the time of evaluation (week 16) 57 patients (47.5%) did not have anemia, while three patients (2.5%) had severe grade. The median level of Hb at baseline visit was 9.61 g/dL. The median level of Hb during the first, second, third, fourth and the fifth visit was in the range of 11 g/dL to 12.9 g/dL, defined as mild anemia (Figure 1).

As multivariate analysis have shown, the difference in median levels of Hb on different visits was statistically significant (p=0.01). Statistically significant difference was found in Hb levels at baseline compare with other study visits (p=0.000024; p=0.000020; p=0.003775). Target Hb level (12 g/dL) was achieved in 21.1% patients at first study visit. These levels were reached in second visit in 35.9% of patients, 37.7% of patients for third visit, and 42.8% patients for fourth study visit. Mean target hemoglobin level compared with the basic study visit was achieved after the second visit or after six weeks of epoetin beta therapy. Hemoglobin levels significantly increased after twelve weeks of epoetin beta treatment. The lowest hemoglobin level was at the basic visit (Figure 1)

One of the most important efficacy points of study was the number of indicated transfusions. As statistical multivariate analyses have shown, we found this number was decreased during epoetin beta treatment. At the first study visit 10 patients (8.3%) received blood transfusion, at second visit 3 patients (2.5%), at third 5 patients (4.2%) and at forth 4 patients (3.3%) received transfusion. The lowest number of patients (1.7%) who needed a blood transfusion was at fifth visit. As well, initial schedule of epoetin beta treatment was 30,000 IU weekly in three divided doses. Due to Hb changes dose of epoetin beta was increased or decreased. These different schedules were noticed during each visit. At the first visit 14 patients (11.7%) required dose changes. During the study doses of epoetin beta were slightly increased (Table 2).

The majority of patients terminated epoetin beta after increased level of hemoglobin or ending chemotherapy according to the protocol.

The safety profile shows that 82 patients (68.3%) did not have any adverse event. In thirty eight patients (31.7%) adverse events were reported. The total number of adverse events was 50. According to seriousness criteria, 44% of total numbers of adverse events were non-serious (Table 3). In majority of cases causal relationship between epoetin beta and adverse event was not related (92%). Four adverse events (8%) were directly related to epoetin beta according to investigators assessment (Table 4).

At the end of the study, 106 patients (88%) were alive and 14 patients (12%) died. In most cases (78.7%) patients died due to cancer progression, one patient had acute cardiorespiratory insufficiency (7.1%) and one patient died due to acute enterocolitis (7.1%).

Table 1: Demographics and patients baseline characteristics

Characteristic	Item	Total
Sex	Female Male	64 56
Age	Median Range	59.9 y +/-11,3 y 27-83 years
Hemoglobin (g/dL)*	Mean	9.61
	Range	7.6-10.9
Blood pressure* (mmHg)	Systolic	127.5
	Diastolic	80.5
Red blood cells*	Mean	3.56
	Range	2 - 4.93
Hematocrit*	Mean	0.296
	Range	0.207-0.385

*parameter values on the basic (first) visit

Table 2: Patient number who need changes of epoetin beta dosage

Number of study visit	No Pts with dose changes	%
I	14	11.7
II	18	15.0
III	20	16.7
IV	16	13.3
V	5	5

Table 3: Adverse events: intensity, relationship (drug and adverse events) and outcomes

Intensity	n	%	Relationship	n	%	Outcome	n	%
mild	8	16.0	probable	1	2.0	recovery	28	56.0
moderate	14	28.0	Possible	3	6.0	ongoing	8	16.0
severe	17	34.0	insignificant	0		unknown	1	2.0
Life-threatening	11	22.0	Not related	46	92.0	death	13	26.0

Table 4: Adverse events related to study drug and outcomes

Adverse events	no	Intensity	Relationship	Outcome
Lip oedema	1	moderate	possible	recovery
Vein thrombosis	1	severe	possible	recovery
CV insufficiency	1	Life-threatening	possible	death
Deep vein thrombosis	1	Life-threatening	probable	death

DISCUSSION

Cancer patients on chemotherapy frequently suffer from different levels of anemia. Severe anemia is common in patients with cancer and metastasis [11]. Blood transfusion is the fastest way to improve cancer anemia related symptoms. From another side there are some serious side effects of transfusion as immunosuppression, hemolytic reactions and thrombotic events. This way of intervention is not followed with QoL stabilization. In most cases physicians prescribe transfusion at the Hb level lower than 8.0 g/dL. Clinical studies of anemic cancer patients show that epoetin increasing hemoglobin levels and reduced the need for blood transfusions [12, 13].

In our multicentric study in Montenegro we included 75 patients with solid tumor (lung cancer, breast cancer, colorectal cancer, gastric cancer, kidney cancer, ovarian cancer, cervical cancer, laryngeal cancer) and 45 patients with hematological malignancies. More patients included in study were females due to breast cancer and gynaecological cancers treated on oncology and radiotherapy clinic.

Our statistical results have shown that epoetin beta at a dose of 30,000 IU per week in three divided doses is safe and can effectively increase Hb levels lowering the need for blood transfusions. The hematocrit values increased significantly during epoetin beta treatment comparable with study of Bogdanosi [14, 15]. The number of patients who need blood transfusion was decreasing during treatment duration with epoetin beta in our study. The median level of Hb at baseline visit was 9.61 g/dL. Difference in median levels of Hb on different visits was statistically significant (p=0.01). Statistically significant difference was found in Hg levels at baseline compare with other study visits. These data shows that Hb values are increasing during the treatment duration and the number of blood transfusion is lower. The target Hb values are reached in second visit in 35.9% of patients, 37.7% patients for third visit, and 42.8% patients for fourth study visit. The therapy with epoetin beta shows efficacy during anemia treatment. Hb levels significantly increased after twelve weeks of epoetin beta. One of the most important efficacy study points was the number of indicated transfusion. We found that indications of transfusion during epoetin beta treatment were reduced. At the first study visit 10 patients (8.3%) received blood transfusion, at second 3 (2.5%), at third 5 patients (4.2%) and at forth 4 patients (3.3%). The lowest number of patients (1.7%) who needed a blood transfusion was at fifth visit. We achieved the most important goal to reduce the number of transfusions due to its short benefit and lot of side effects.

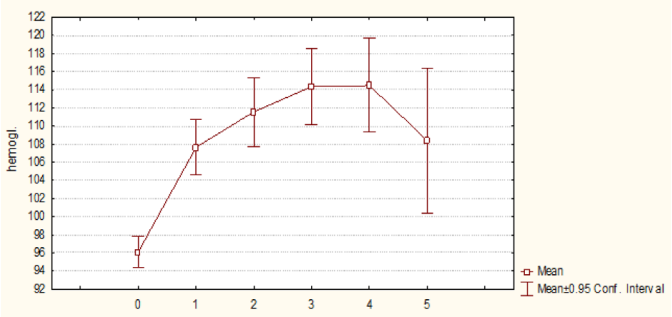

Figure 1: Median hemoglobin levels (g/L) during study visits (0–5).

Initial schedule of epoetin beta treatment was 30,000 IU weekly in three divided doses. Variable levels of hemoglobin in cancer patients require epoetin beta dosing changes. These changes cause different epoetin beta dosing regimens which were noticed during scheduled visits. At the first visit 14 patients (11.7%) required dose changes. During study doses were slightly increased. These shows that drug is efficient in terms of increasing of Hg level. In our study safety profile shows that 82 patients (68.3%) have not any adverse event. In 38 patients (31.7%) adverse events were reported. The total number of adverse event was 50. According to seriousness

criteria 44% of total numbers of adverse events were non-serious. In majority of cases causal relationship between epoetin beta and adverse event was not related (92%). Four adverse events (8%) were directly related to epoetin beta according to investigators assessment. In terms of intensity of side effects in our Montenegro study 44% were mild or moderate and severe was in 34% of patients on epoetin beta. After finishing the study 88% of patients were alive and 12% died due malignant disease. In the majority of cases (78.7%) patients died due to cancer progression. These results shows that appropriate treatment with chemotherapy in support with anemia correction could be beneficial for patients with different cancer types. The results of the study are comparable with data on safety of epoetin beta obtained in results from controlled clinical trials [16]. Also the benefits of this clinical study are that investigators routinely indicated supportive and symptomatic therapies which are very important for cancer patients. The correction of chemotherapy related anemia increasing QoL of oncology patients.

CONCLUSION

Epoetin beta has proven efficacy and safety across a wide range of solid and non-myeloid hematological malignancies. Epoetin beta is effective at increasing hemoglobin levels and reducing transfusion needs in patients with cancer. Our study suggested that patients receiving chemotherapy may be a subgroup of cancer patients with the most potential benefit of epoetin beta treatment. Safety data confirmed favorable epoetin beta safety profile. Careful clinical assessment is a key component of anemia management.

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Vladimir Todorovic – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
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The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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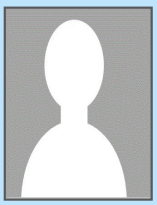

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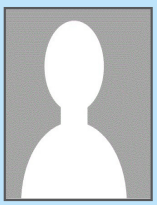

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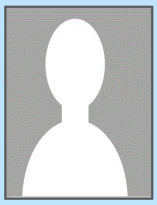
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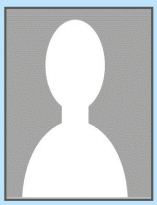
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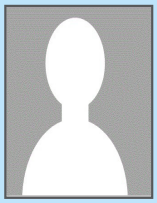
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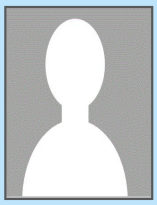
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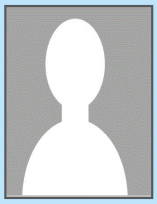
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