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# ERYTHROPOIETIN AS AN INDEPENDENT PROGNOSTIC FACTOR IN MYELODYSPLASTIC SYNDROMES

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***Aim:*** **To assess the level of erythropoietin (EPO) in blood sera of patients with different subtypes of myelodysplastic syndromes (MDS) from different risk subgroups and to determine its prognostic role.** ***Materials and Methods*****: EPO was measured by enzyme-linked immunosorbent assay in peripheral blood of 54 patients with different MDS subtypes according to the French–American–British (FAB) classification. The comparison group consisted of 15 healthy individuals. Complete blood count (hemoglobin, leukocyte and platelet levels) was determined and bone marrow cells were characterized morphologically. The overall and leukemia-free survivals were estimated by Kaplan — Meier method.** ***Results:*** **The level of EPO in MDS was reliably higher in comparison with healthy persons ($p < 0.01$, Mann — Whitney test). No statistically significant difference was found in serum EPO concentration between the groups of patients with low- and high-risk MDS (603.5 pg/ml *vs* 721.0 pg/ml; $p > 0.05$). In transfusion-dependent patients, the level of EPO was significantly higher than in other patients, which may be due to increased endogenous EPO secretion resulting from chronic hypoxia. A negative correlation was revealed between EPO level and Hb level as well as between EPO level and percentage of blast cells in bone marrow in high-risk MDS patients but not in patients with less aggressive variants of MDS. Instead, patients with low-risk MDS had a negative relationship between concentrations of EPO and tumor necrosis factor alpha ($p = 0.06$, Kendall's tau test). No significant difference was found between EPO concentration in cases differing by bone marrow cellularity or the presence of cytogenetic abnormalities. An EPO concentration below 200 pg/ml was a predictor of shorter overall survival in patients with all MDS subtypes ($p < 0.05$, Mann — Whitney test). In patients with all FAB disease subtypes, there was no relationship between the leukemia-free survival and serum EPO concentration.** ***Conclusion:*** **This study shows that lower serum EPO level may be considered as one of the additional adverse prognostic factors in MDS patients.**
***Key Words:*** **myelodysplastic syndromes, anemia, erythropoietin, survival.**

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The ineffective hematopoiesis typical for myelodysplastic syndromes (MDS) results from a number of disorders in bone marrow (BM), including genetic, epigenetic and immunomodulatory changes in hematopoietic/progenitor cells as well as the imbalance in relationship between hematopoietic and stromal cells with abnormal release of growth factors and chemokines [1–3]. The most common manifestation of MDS is anemia with quite complex pathophysiology involving several factors. For example, the activation of macrophages and increased production of cytokines cause shortening of the erythrocyte life, and the impaired reutilization of iron in BM and abnormal production of endogenous erythropoietin (EPO) result in anemia [4].

Several mechanisms of the anemic syndrome development in MDS patients have been proposed. One of the most important pathogenetic aspects regarding anemia in MDS is the cytokine component [5, 6]. According to many researchers, the production of cytokines, and in particular their concentration in blood serum, is regulated by BM niches that control hematopoietic stem cells proliferation and quiescence [7]. In turn, BM niche contains a diverse number of stromal cells, including macrophages, fibroblasts and osteoblasts, as well as the blood vessels and the elements of the extracellular matrix [8, 9].

EPO is considered as one of the main cytokines regulating hemopoiesis and is the first factor that responds to the reduction of hemoglobin in patients with MDS. The understanding of the physiological functions of EPO has significantly evolved over the last few decades. Its main functions are to stimulate the proliferation, differentiation and maturation of erythroid cells, to inhibit their apoptosis, to regulate iron metabolism, neutralizing the inhibitory effect of cytokines on hematopoiesis [10]. Normally, endogenous EPO is produced by peritubular cells of renal cortex (up to 90%) and liver cells (10–15% of the total production) and is controlled via oxygen-dependent mechanisms. The decreased EPO level is associated not only with MDS but also with anemia of other genesis [10, 11]. Interferon-gamma, tumor necrosis factor alpha, interleukin 1 and interleukin 6, have been shown to inhibit erythropoiesis *in vitro* and *in vivo*, decreasing EPO production [12–14].

The studies on the EPO role in the pathogenesis of MDS, in particular in the mechanisms of ineffective hematopoiesis, started as early as in the 1980s. EPO receptors are detected in the erythroid burst-forming

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*Abbreviations used*: AL – acute leukemia; BM – bone marrow; EPO – erythropoietin; MDS – myelodysplastic syndromes; OS – overall survival; RA – refractory anemia; RAEB – refractory anemia with excess of blasts; RAEB-t – refractory anemia with excess of blasts in transformation; RARS – refractory anemia with ring sideroblasts; TGF-β – transforming growth factor-β; TNF-α – tumor necrosis factor-α.

unit. Their expression increases during maturation of erythroid precursors, while EPO receptors are not detected on more mature erythroid cells. At present, it has been proven that serum EPO deficiency is not a cause of ineffective erythropoiesis [15]. Alternatively, the ineffective erythropoiesis is attributed to intracellular defects of EPO-induced antiapoptotic pathways and by excessive stimulation of proapoptotic signals [16, 17]. Serum EPO concentrations are significantly higher in transfusion-dependent patients while this was not confirmed in high-risk patients. It is worth to mention that serum EPO level correlated with a significant reduction in overall survival (OS) [18]. Negative correlation between serum EPO and hemoglobin concentration was observed [19, 20].

A number of prognostic factors for MDS are described, but there is no sufficient information regarding the relationships between these markers and life expectancy or low- and high-risk groups due to the various mechanisms of development and progression in different MDS subtypes. Therefore, this question is relevant and has not only scientific but also practical significance.

## MATERIALS AND METHODS

Patients with MDS of different subtypes according to the FAB classification were observed and treated in the SI "Institute of Blood Pathology and Transfusion Medicine of NAMS of Ukraine" and the Lviv Communal Municipal Clinical Hospital № 5 in 2010–2015 were included into the study. All patients gave their informed consent for participation in the study and the processing of their depersonalized clinical and biochemical data.

The group of patients with refractory anemia (RA) included 26 people (median age 59 years (48–77), 5 patients were diagnosed with refractory anemia with ring sideroblasts (RARS) (median age 69 years (54–71), 21 patients had refractory anemia with excess of blasts (RAEB) (median age 61 years (30–81) and 2 patients suffered from refractory anemia with excess of blasts in transformation (RAEB-t) (aged 32 and 76). Control group included 15 healthy donors with median age of 60 years (35–69). The studied groups were formed based on the risk of transformation to acute leukemia (AL), namely low-risk group (RA, RARS) and high-risk group (RAEB, RAEB-t), taking into consideration the similarity of clinical, hematological, cytogenetic parameters and the course of the disease within each of these groups.

Blood samples were taken from MDS patients with different FAB subtypes immediately before transfusion or 7 days after the last blood transfusion in order to reduce the false results, since the production of endogenous EPO to certain degree depends on the hemoglobin level.

Endogenous EPO concentration in serum was measured by enzyme-linked immunosorbent assay using Erythropoietin-IFA-Best kit (Vector Best, Russian Federation) according to the manufacturer's instruction. The optical density was measured using enzyme analyzer Multiscan EX (Thermo Fisher Scientific, USA) at a wavelength of 450 nm.

Complete blood count (hemoglobin, leukocyte and platelet levels) was determined automatically on a CellDynRuby hematology analyzer (Abbott, USA). The morphological characterization of BM cells (in particular, signs of dyshemopoiesis of the three lineages) and number of blasts in BM were assessed using a light microscope.

Serum tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) levels were determined by enzyme-linked immunosorbent assay and kits for detection of TNF-α (BIOSOURCE, Belgium) and TGF-β (ELISA kit, Germany) using immunoassay Multiscan EX analyzer at a wavelength of 450 nm.

Statistical analysis was performed using software package STATISTICA 6.0, by StatSoft Inc. (USA). Parametric data were presented as median [lower-upper quartile] (minimum-maximum). The duration of overall and leukemia-free survival were estimated using the Kaplan — Meier method. The log-rank test or Cox F-test was used to compare survival in the two groups. Cox proportional hazard regression was used to determine the most significant independent prognostic factors affecting survival. The breakdown points for parametric indicators were determined using sequential Wald analysis. The interdependence between the indices of paired studies determined the rank correlation (Kendall's tau [τ] test).

## RESULTS AND DISCUSSION

Serum concentration of EPO did not differ significantly between MDS patients of low-risk group (median 603.5 pg/ml with fluctuation ranges from 51.0 to 2022.0 pg/ml) and high-risk group (median reached 721.0 pg/ml). However, in both groups EPO level was markedly different from such in control group ($p < 0.05$) (Fig. 1).

When EPO concentration was assessed in relation to sex of patients, no significant difference was revealed. Median serum EPO in women reached 781 pg/ml, in men — 446 pg/ml (Mann — Whitney test, $p = 0.46$).

Statistically significant difference in EPO concentration was revealed in patients from group of high-risk

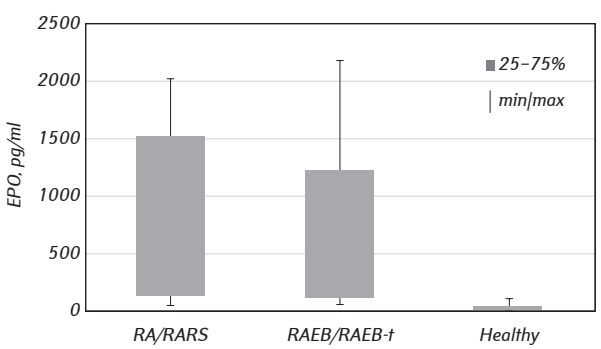


**Fig. 1**. Serum EPO concentration in patients from low-risk and high-risk groups. The difference in comparison with healthy donors was significant ($p < 0.05$, Mann — Whitney test)

MDS (RAEB/RAEB-t) with hemoglobin level below and above 80 g/l. In patients with more severe anemia, EPO level reached 765.5 pg/ml *vs.* 124 pg/ml in patients with less profound anemia (Mann — Whitney test, $p < 0.05$). Such tendency was not observed in patients with low-risk MDS (RA/RARS). In this group, patients with higher hemoglobin content had EPO concentration at a level 614 pg/ml (ranging from 51 pg/ml to 2022 pg/ml), which substantially did not differ from such in patients with more severe anemia who had median EPO level of 801.5 pg/ml (ranging from 51 pg/ml to 2022 pg/ml) (Mann — Whitney test, $p > 0.05$).

In order to determine possible association between the concentration of the cytokine and BM cellularity, all patients were divided into three groups, namely with hypocellular, normocellular and hypercellular BM. The highest EPO concentration was observed in patients with hypercellular BM, median was 781 pg/ml (506–2179 pg/ml). Nevertheless, the maximum EPO level did not change significantly in comparison with previous group and was 2027 pg/ml in group of normocellular and 2179 pg/ml in group of hypercellular BM. There was no marked difference in EPO concentration of this cytokine between different groups depending on BM cellularity ($p > 0.05$, Mann — Whitney test) (Fig. 2).

Taking into consideration that cytogenetic changes in hematopoietic cells play crucial role in the course and prognosis of MDS, we analyzed EPO level depending on the presence or absence of significant chromosomal aberrations in BM cells. EPO level did not differ significantly between the groups with unchanged karyotype and with solitary abnormalities and reached 857 pg/ml and 1093 pg/ml respectively ($p > 0.05$, Mann — Whitney test).

Analysis of correlation between EPO concentration and some constitutional and hematological parameters was performed. In patients with low-risk MDS, EPO concentration did not correlate with demographic data, peripheral blood or BM parameters. Contrary to this, in patients with high risk of transformation, a negative correlation between the hemoglobin level and EPO concentration ($\tau = -0.15$; $p = 0.039$) and reliable relationship between BM blasts percentage and EPO concentration ($\tau = -0.45$; $p = 0.01$) were revealed (Table).

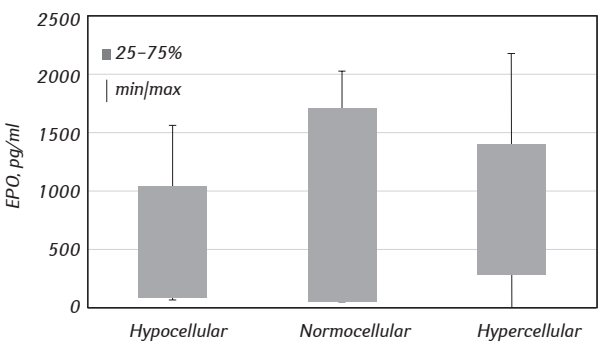


**Fig. 2**. EPO level in patients with different MDS subtypes depending on BM cellularity.

**Table.** Correlation between EPO concentration and peripheral blood, BM parameters and cytokines (patients with RA/RARS and RAEB/RAEB-t)

| Parameter | RA/RARS | | RAEB/RAEB-t | |
|---|---|---|---|---|
| | EPO, pg/ml | | | |
| | τ | p | τ | p |
| Age | 0.08 | 0.603 | –0.23 | 0.207 |
| Hb level | –0.01 | 0.993 | –0.15 | **0.039** |
| Platelets | 0.09 | 0.559 | 0.133 | 0.471 |
| BM blasts | 0.09 | 0.574 | –0.45 | **0.01** |
| TNF-α | –0.13 | 0.06 | 0.19 | 0.35 |

*Note*: τ – Kendall correlation coefficient

Negative correlation was revealed between EPO level and risk of transformation into AL in accordance with prognostic scale IPSS-R ($\tau = -0.45$; $p = 0.066$) and IPSS ($\tau = -0.06$; $p = 0.006$). It was demonstrated that EPO concentration was significantly higher in patients with very low, low and intermediate-1 risk of transformation.

The study of the effect of EPO as a parametric variable on OS using the proportional regression model of risk in RA/RACS group showed no reliable relationship between serum EPO concentration and survival of patients ($p = 0.51$) in contrast to patients from high-risk group ($p = 0.004$)

Based on results of a Wald's sequential analysis, an EPO concentration of 200 pg/ml was chosen for high-risk MDS patients as a threshold, at which the difference in OS between the study subgroups was most significant. In this regard, a group of patients was divided into two subgroups: those with an EPO level of less and more than 200 pg/ml. Contrary to literature data, median OS in patients with higher EPO concentration was 36.9 months (lower quartile 19.1 months), in comparison with subjects with lower EPO level, who had median OS 6.7 months (OS in 25% of patients was 1.9 months). In this respect, low serum EPO concentration in patients with aggressive subtypes of MDS might be considered as an unfavorable factor for OS in this population.

Lower EPO level is an independent prognostic marker for predicting the survival in patients with high-risk MDS. In contrast to the literature data, the survival of our patients with higher EPO level was significantly longer. The expected cumulative 2-year survival in high-risk MDS patients with EPO below 200 pg/ml was 8% *vs*. 57% in patients with an EPO concentration above this threshold level. The 3-year survival of patients with high EPO concentration was 37%, 4-year survival was nearly 9%, 5-year survival — 4%.

In patients with low-risk MDS, only slight difference was found in 2-year survival in studied subgroups regarding the concentration of endogenous EPO. Thus, predicted survival (2 years) in patients with higher EPO was 54.0% *vs*. 45.9% in subjects with lower EPO concentrations ($p < 0.05$, Cox F-test). At the same time, a significantly longer duration of 4-year and 5-year survival was observed in patients with an EPO level above 200 pg/ml, and the proportion of surviving patients was 27.8% *vs.* 6.1% and 15.6% *vs.* 3.1%, respectively.

Consequently, we have analyzed the relevance of serum EPO levels as a prognostic marker in patients

with *de novo* MDS. Our results showed that patients with different MDS subtypes according to FAB classification have statistically significant differences in serum EPO level at the time of diagnosis that correlated with survival.

Patients with all MDS subtypes had significantly higher EPO level in comparison with healthy donors. However, since median Hb level in two groups of patients did not differ, there was no marked distinction in EPO level regarding disease risk profile. Moreover, in patients with lower Hb EPO concentration was higher, which might indicate enhanced endogenous EPO secretion in response to hypoxia. Our results in this respect are consistent with the literature data [20]. As pointed out by Jelkmann [8], response to hypoxia *in vivo* is a dynamic process, meaning that EPO concentration increases following anemic or hypoxemic stimuli, with further decrease despite continuous hypoxia. This corresponds with our data demonstrating the significant changes in EPO concentration in patients with less aggressive and more aggressive MDS subtypes. It is known that in patients with different MDS subtypes the mechanisms of cytopenia development and the duration of anemia are distinct. Thus, in low-risk MDS, EPO enhances differentiation of erythroid and myeloid progenitors. At the same time its level correlates with TNF-α, TGF-β, which in turn exert inhibitory effects on stem hematopoietic cells, as proven by Isufi *et al*. [21]. Increased production of TNF-α and TGF-β in early stages of MDS, which is associated with an EPO increase in response to hypoxia, as well as disturbances of adhesion of stem and stromal cells, represents the pathogenetic basis for the development of anemic syndrome in these patients (due to apoptosis activation). Contrary to above-mentioned, in patients with high-risk MDS, increased production of interleukin-6 by blast cells and enhanced production of vascular endothelial growth factor with activation of BM angiogenesis underlie the occurrence of anemia and disease progression.

The negative correlation revealed between the levels of TNF-α and EPO confirms inhibitory effect of proinflammatory cytokines on EPO secretion not only in patients with MDS [14] but also in patients with anemia of chronic disease widely described in the literature [12, 13]. However, pathogenesis of anemia in MDS is rather complex and involves not only cytokine-mediated mechanisms but also multiple other factors. Therefore, this interdependency is an unsettled and debatable issue.

We have not shown a reliable relationship between EPO concentration and BM cellularity. This is quite expectable since EPO is produced largely in kidneys and not by hematopoietic stem cell or BM microenvironment. On the other hand, based on a series of studies, scientists have concluded that reduced oxygen transport to tissues or increased body oxygen demand stimulates EPO excretion [20]. However, based on the study of changes in the concentration of EPO in the dynamics, scientists have put forward the theory that the decrease in EPO content in plasma is associated with its increased utilization by BM cells. Subsequent studies in this direction have refuted this theory proving that the uptake of EPO in BM has no importance for the EPO metabolism in comparison with its daily renal production and BM cannot be considered as a place of EPO disposal or inactivation. Therefore, correlation between EPO concentration and BM cellularity could not been confirmed.

Our study aimed to analyze the diagnostic significance of serum EPO in a group of patients with *de novo* MDS in order to evaluate its relationship with the risk of transformation to AL, and with OS of the patients. This information allows us to determine the potential to use EPO as a prognostic factor.

The issue of the correlation of EPO level with OS in patients with different MDS subtypes has not been sufficiently covered in the available literature. Only some of researchers consider association between lower OS of these patients and high endogenous serum EPO concentration [19], which is not compatible with our results. OS in our high-risk MDS patients was significantly longer at higher EPO concentrations. Such a difference with low-risk MDS may be due to the involvement of other mechanisms in pathogenesis of more aggressive MDS subtypes. Therefore, the issue of heterogeneity of this disease remains relevant and requires a differentiated approach not only in diagnostics but also in therapeutic tactics.

Important part of the management of all MDS patients is not only improving the quality of life, but also reduction of the risk of disease transformation. Therefore, scientists are exploring the factors that determine the likelihood of such transformation. The literature data shows that a high EPO level is associated with a shortened leukemia-free survival [17, 19]. However, we did not find a relationship between the leukemia-free survival and serum EPO level neither in patients with RA/RARS nor in the RAEB/RANBt group. This is probably due to a small number of patients with a determined serum EPO level and requires further research.

In available literature, there is no clear numerical value of EPO concentration that would be prognostic of survival. We have found that OS in high-risk MDS patients with higher EPO concentrations was more than 5-fold higher in comparison with patients with low EPO level. Thus, serum EPO concentration less than 200 pg/ml is suggested to be another negative prognostic factor for OS in patients with high-risk MDS.

Our study showed the importance of determining serum EPO as an independent prognostic factor in patients with primary MDS, both low- and high-risk according to the IPSS classification. The analysis revealed that an EPO level above 200 pg/ml in patients with high-risk MDS could be considered as a marker of a poor prognosis associated with a shortened OS. It becomes apparent that the same factors differently affect the duration of OS and the rate of leukemic transformation in different FAB subtypes and risk

groups of MDS. In spite of the large number of continuously updating prognostic scales, the issue of MDS prognosis remains relevant and encourages the use of differentiated approaches to the further investigation of prognostic factors and the development of new prognostic scales separately for low- and high-risk MDS patients.

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## ЕРИТРОПОЕТИН ЯК НЕЗАЛЕЖНИЙ ПРОГНОСТИЧНИЙ ФАКТОР У ХВОРИХ НА МІЄЛОДИСПЛАСТИЧНІ СИНДРОМИ


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***Мета**:* Визначити рівень еритропоетину (ЕПО) в сироватці крові хворих на різні підтипи мієлодиспластичних синдромів (МДС), що складають різні підгрупи ризику, та оцінити прогностичну роль цього показника. ***Матеріали та методи***: Концентрацію ЕПО вимірювали методом твердофазного імуноферментного аналізу в зразках периферичної крові 54 хворих на різні підтипи МДС відповідно до ФАБ класифікації. Група порівняння складалася з 15 здорових осіб. Визначали вміст гемоглобіну, лейкоцитів та тромбоцитів. Клітини зразків кісткового мозку характеризували морфологічно. Загальну та безрецидивну виживаність розраховували за методом Каплана — Мейєра. ***Результати***: Рівні ЕПО у хворих на МДС були вірогідно вищими в порівнянні зі здоровими особами ($p < 0.01$, критерій Манна — Уітні). Не було виявлено статистично вірогідної різниці за концентрацією ЕПО між групами хворих на МДС низького та високого ступеня ризику (603,5 пг/мл в порівнянні з 721 пг/мл; $p > 0.05$). У хворих, залежних від гемотрансфузій, рівні ЕПО були вірогідно вищими в порівнянні з іншими пацієнтами, що може бути обумовлено підвищенням секреції ендогенного ЕПО, спричиненим хронічною гіпоксією. У хворих на МДС групи високого ризику була виявлена негативна кореляція між рівнями ЕПО та гемоглобіну, а також між рівнями ЕПО та відсотком баластних клітин у кістковому мозку. Такої кореляції не відзначали у хворих з менш агресивними варіантами МДС. Натомість у пацієнтів з МДС групи низького ризику відзначали негативну кореляцію між концентраціями ЕПО та фактора некрозу пухлин альфа ($p = 0.06$, критерій тау Кендалла). Не було помічено суттєвої різниці у рівнях ЕПО між випадками, що різняться за клітинністю кісткового мозку або наявністю цитогенетичних аномалій. Концентрацію ЕПО нижче за 200 пг/мл можна розглядати як предиктор меншої