Can red cell distribution width be a new parameter for predicting higher CD34+ cell count in the harvest?

Eritrosit dağılım aralığı üründeki daha yüksek CD34+ hücre sayısını öngördüren yeni bir parametre olabilir mi?

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ÖZET

GİRİŞ ve AMAÇ: Eritrosit dağılım aralığı (RDW) anemi ayırıcı tanısında kullanılan basit ve ucuz bir parametredir fakat diğer hastalıklarla ilişkisi giderek artan oranda bildirilmektedir. Transplantasyon pratiğinde en sık kullanılan hematopoietik kök hücre kaynağı periferik kandır ve kök hücre mobilizasyonunu etkileyen birçok faktör tanımlanmıştır. Çalışmamızda RDW ile üründeki CD34+ hücre sayısı arasında bir ilişki bulmayı amaçladık.

YÖNTEM ve GEREÇLER: Çalışmaya 50 hasta dahil edildi. Tanılar multipl miyelom (n=32), non Hodgkin lenfoma (n=9), Hodgkin lenfoma (n=6), primer amiloidoz (n=1), Waldenström makroglobulinemisi (n=1) ve germ hücreli testis tümörü (n=1) idi. Mobilizasyon rejimleri siklofosfamid+granülosit koloni stimule edici faktör (G-CSF), tek başına G-CSF, etoposid+G-CSF ve kurtarma tedavisi+G-CSF şeklindeydi. RDW'nin üründeki CD34+ kök hücre sayısına etkisini değerlendirmek için 16 eşik değer alınarak hastalar 2 gruba ayrıldı.

BULGULAR: Periferik kan ve üründeki CD34+ hücre sayısı açısından 2 grup arasında istatistiksel olarak anlamlı farklı bulunmamasına rağmen RDW'si yüksek olan grupta sayılar daha düşüktü. RDW ile periferik kan ve üründeki CD34+ hücre sayısı arasında korelasyon saptanmadı.

TARTIŞMA ve SONUÇ: Bildiğimiz kadarıyla çalışmamız kanser hastalarında RDW ile kök hücre mobilizasyonu arasındaki ilişkiyi değerlendiren ilk çalışmadır. Sonuçlarımız kök hücre mobilizasyonunun RDW'nin anemi dışı kullanım alanlarından biri olabileceğini düşündürmüştür.

Anahtar Kelimeler: eritrosit dağılım aralığı, mobilizasyon, hematopoietik kök hücreler

ABSTRACT

INTRODUCTION: The red cell distribution width (RDW) is a simple and unexpensive parameter for differential diagnosis of anemias. However, the number of articles mentioning about the relationship between RDW and human disorders is increasing. In transplantation practice, peripheral blood is the most common source of hematopoietic stem cells and many factors affect the success of mobilization. In this study, we tried to find a relationship between increased RDW and CD34+ cell count in the harvest.

METHODS: Fifty patients were included in the study. Diagnosis were multiple myeloma (n=32), non Hodgkin lymphoma (n=9), Hodgkin lymphoma (n=6), primary amyloidosis (n=1), Waldenstrom's macroglobulinemia (n=1) and testicular carcinoma (n=1). Mobilization regimens were cyclophosphamide plus granulocyte colony stimulatig factor (G-CSF), G-CSF alone, etoposide plus G-CSF and salvage chemotherapy plus G-CSF. RDW was not correlated with peripheral blood CD34+ cell count and CD34+ cell count in the harvest. Above 16% was set as a cut-off for increased RDW and patients were divided into 2 groups.

RESULTS: Although peripheral blood CD34+ cell count and CD34+ cell count in the harvest were not different statistically between 2 groups, the numbers were lower in the increased RDW group. RDW was not correlated with peripheral blood CD34+ cell count and CD34+ cell count in the harvest in both groups.

DISCUSSION AND CONCLUSION: To our knowledge, this is the first study evaluating the relationship between RDW and stem cell mobilization in cancer patients. It seems reasonable to use RDW far beyond the differential diagnosis of anemias and stem cell mobilization can be a potential candidate.

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Keywords: red cell distribution width, mobilization, hematopoietic stem cells

INTRODUCTION

The number of articles investigating the relationship between RDW and human disorders has exponentialy increased over the past decades. RDW has been investigated in a number of cardiovascular diseases and proposed as a predictive biomarker of poor outcomes (1-3). Increased RDW has been found associated with acute pulmonary embolism, deep vein thrombosis and chronic thromboembolic pulmonary hypertension (4-6). An association between increased RDW and low estimated glomerular filtration rate and high mortality has been shown in several studies (7-9). Malignant obstructive jaundice, acute and chronic hepatitis B, non-alcoholic steatohepatitis and cirrhosis are some of the liver diseases found associated with increased RDW (10-12). Increased RDW was associated with complicated hospitalization and high mortality in community acquired pneumonia and presence of right ventricular failure in chronic obstructive pulmonary disease (13). RDW has also been found increased in various malignancies such as colorectal, breast, lung etc. (14-15). Prognostic significance of RDW in hematological malignancies is scarce (16-17).

Hematopoietic stem cell transplantation is a potential curative therapy for various hematological malignancies and several factors affecting the results of hematopoietic stem cell mobilization are described. In this study, we tried to find a relationship between RDW and the stem cell count in the harvest.To our knowledge, increased RDW is associated with poor stem cell mobilization in patients with advanced chronic heart failure [18] but there is no report about the effect of RDW to mobilization in malignant diseaeses.

MATERIALS AND METHODS

Fifty patients who underwent stem cell mobilization between March 2014 and October 2015 are included in the study. Mean age was 56.82± 10 years, 28 (56%) patients were male and 22 (44%) patients were female. Diagnosis were multiple myeloma (n=32), non Hodgkin lymphoma (n=9), Hodgkin lymphoma (n=6), primary amyloidosis (n=1), Waldenstrom's macroglobulinemia (n=1) and testicular carcinoma (n=1). Mobilization regimens were cyclophosphamide (4 g/m^2/day plus G-CSF 5 mcg/kg/day in 35 (70%) patients, G-CSF 10 mcg/kg/day alone in 2 (4%) patients, etoposide 600 mg/m^2 plus G-CSF 5 mcg/kg/day in 2 (4%) patients and salvage chemotherapy plus G-CSF 5 mcg/kg/day in 11 (22%) patients. Five (10%) patients had a history of radiotherapy. 20 (40%) patients had comorbidities (hypertension, diabetes, asthma, chronic obstructive pulmonary disease, renal failure, coronary artery disease, hypothyroidism, prostat carcinoma, tonsil carcinoma, atrial fibrillation, fibromyalgia, irritable colon, cerebrovascular disease). Bone marrow infiltration for patients except myeloma was found in 6 (35%) patients. Patients received mean 1.61 ±0.60 lines and 4.94± 2.60 courses of chemotherapy. RDW was measured in blood samples collected in EDTA tubes which were analyzed with an automated hematology analyzer system (Coulter LH 750 Hematology Analyzer, CA, USA). Normal RDW values ranged between 11.80% and 14.30% according to our laboratory standards. Biochemical parameters were determined with standard procedures. All blood samples were collected on first day of apheresis or maximum 1-3 days before apheresis. Laboratory parameters are shown in Table 1. Stem cells were collected during mean 1.82±0.75 days. Since it shows high anisocytosis (19), above 16% was set as a cut-off for increased RDW and patients were divided into 2 groups. The research protocol has been approved by local ethical committee and performed in accordance with the ethical standards laid down in the Declaration of Helsinki. All patients gave informed consent prior to their inclusion in the study.

Statistics

All data analyses were performed using commercially available software (PASW Statistics 22, SPSS, Inc., Chicago, IL; and SigmaStat 3.5, Systat Software, Inc., San Jose, CA). Continuous normally distributed

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variables were demonstrated using n (sample size) and mean and standard deviation, continuous non normally distributed and categorical variables using n (sample size) and median and 25th and 75th percentiles. Score variables between 2 groups were compared using the Mann-Whitney U test. Spearman correlation analysis was used to determine correlations among non-normally distributed variables. Chi-square analyses were used for categorical variables. $p < 0.05$ was accepted as statistically significant. All data analyses were performed using commercially available software (PASW Statistics 22, SPSS, Inc., Chicago, IL).

RESULTS

RDW was not correlated with peripheral blood CD34+ cell count (r=0.064, p=0,750, n=28) and CD34+ cell count in the harvest (r=-0.14, p=0,340, n=50). Other parameters previously reported to affect stem cell mobilization (age, weight, number of chemotherapy courses before mobilization, hemoglobin, white blood cell count, absolute neutrophil count, absolute lymphocyte count, platelet count, albumin, lactate dehydrogenase) were also evaluated. Peripheral blood CD34+ cell count (r=0.694, p=0,001, n=50) and the number of chemotherapy courses before mobilization (r=-0.451, p=0,008, n=28) were found as the only parameters that affect CD34+ cell count in the harvest. In order to investigate the effect of increased RDW on the CD34+ cell count in the harvest; above 16 was set as a cut-off for increased RDW and patients were divided into 2 groups. Sex, primary diagnosis, stage, bone marrow infiltration, mobilization regimen, chemotherapy courses, radiotherapy, comorbidities, number of leukapheresis days were not different between two groups. Comparison of laboratory parameters are shown in Table 2. Lactate dehydrogenase (LDH) was the only parameter different between 2 groups. It was found higher in the increased RDW group (p=0,005). Although peripheral blood CD34+ cell count and CD34+ cell count in the harvest were not different statistically between 2 groups, the numbers were lower in the increased RDW group. RDW was not correlated with peripheral blood CD34+ cell count and CD34+ cell count in the harvest in both groups.

Table 1: Laboratory Parameters

Parameter	Mean value ± S. D.
Hemoglobin (g/dl)	9.96±10.00
White blood count ($x10^9$/L)	9.61±6.98
Absolute neutrophil count ($x10^9$/L)	7.16±6.78
Absolute lymphocyte count ($x10^9$/L)	0.62±0.51
Platelet ($x10^9$/L)	48.44±42.56
Red cell distribution width (%)	15.88±2.39
Albumin (mg/dl)	3.71±0.42
Lactat dehydrogenase(IU/L)	543.62±356
Peripheral blood CD34+ cell count (/μl)	48.81±55.47

S.D. : Standard deviation

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Table 2: Comparison of Laboratory Parameters for Increased and Normal Red Cell Distribution Width (RDW)

Parameter	Mean±S. D. (RDW< 16) n=26	Mean±S. D. (RDW ≥16) n=24	p
Hemoglobin (g/dl)	10.12±1.38	9.79±1.74	0,236
White blood count ($x10^9$/L)	8.77±5.21	10.52±8.52	0,573
Absolute neutrophil count ($x10^9$/L)	6.52±5.48	7.85±8.02	0,587
Absolute lymphocyte count ($x10^9$/L)	0.61±0.58	0.62±0.43	0,525
Platelet ($x10^9$/L)	43.5±36.69	53.79±48.35	0,547
Albumin (mg/dl)	3.82±0.45	3.59±3.59	0,058
Lactat dehydrogenase (IU/L)	421.35±226.61	676.08±423.13	0,005*
Peripheral blood CD34+ cell count (/μl)	54.97±62.33 (n=17)	39.28±43.90 (n=11)	0,437
CD34+ cell count in the harvest ($x10^6$/kg)	10.48±5.94	8.07±5.01	0,080

S.D. : Standart deviation

DISCUSSION

One of the leading technical issues in routine assessment of RDW is that the reference range is highly analyzer dependent and hampers the use of universal reference ranges. Besides pathological causes there are physiological determinants of increased RDW such as erythropoietin stimulation, ageing, black ethnicity, physical exercise and pregnancy (19). The only possible physiological determinant was age for our patients however it was not accepted as a physiological determinant of increased RDW because of the similarity between 2 groups (58 vs 55.60, p>0.05). The relationship between RDW and gender appears contradictory across different epidemiological investigations [19]. Gender was not also a physiological determinant according to our results. Using different analyzers can be a issue but our results were completely obtained from the same analyzer.

An increased RDW mirrors a profound deregulation of erythrocyte homeostasis and survival, which may be caused by a variety of abnormalities such as shortening of telomeres length, oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, dyslipidemia and abnormality of erythropoietin function. All these conditions are important prognostic factors for severe morbidity and death (19). It could be valuable to assess the relationship between RDW and inflammatory markers, hypertension, dyslipidemia, nutritional status and/or erythrocyte fragmentation in a clinical study but we did not evaluate this point as a limitation of our study. On the other hand, Lippi et al (20) discovered that the relationship between high RDW and increased levels of inflammatory indicators including CRP and

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erythrocyte sedimentation rate is independent of other associated comorbidities.

Being a single center study with small patient size and retrospective patient enrollment are other limitations of our study.

In our study; sex, primary diagnosis, stage, bone marrow infiltration, mobilization regimen, chemotherapy courses, radiotherapy, comorbidities, number of leukapheresis days were not different between two groups. As a result we suggested that these paramaters did not affect stem cell colection and RDW affected the results independently although the difference was not found statistically significant.

Since it shows high anisocytosis above 16% was set as a cut-off for increased RDW in our study. To our knowledge %16 is the highest cut off for increased RDW reported in literature. Some cut off values reported are ≥13.60% (20), >14.50% (21) and >13.75% (22). We hypothesized that setting above 16% as a cut off may change results of some previously reported studies.

Although peripheral blood CD34+ cell count and CD34+ cell count in the harvest were not different statistically between 2 groups, the numbers were lower in the increased RDW group. RDW was not correlated with peripheral blood CD34+ cell count and CD34+ cell count in the harvest in both groups. We think the difference can reach to statistical significance in larger studies.

To our knowledge, this is the first study evaluating the relationship between RDW and stem cell mobilization in cancer patients. Although it has not been definitely established whether increased RDW is a risk factor or an epiphenomenon of an underlying biological and metabolic imbalance, it seems reasonable to suggest using RDW far beyond the differential diagnosis of anemias. Stem cell mobilization can be a potential candidate in this era.

Conflict of interest: None

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