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Research paper

Association of red cell distribution width with clinical outcomes in myelodysplastic syndrome

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ABSTRACT

Studies showed red cell distribution width (RDW) can improve the detection of morphological changes in red blood cells and the understanding of their contribution to dyserythropoiesis in myelodysplastic syndrome (MDS). The purpose of the study was to evaluate dyserythropoiesis in MDS by RDW analysis and to explore the utility of RDW in clinical practice. We retrospectively analyzed laboratory and clinical data of 101 patients (59 patients was refractory anemia (RA) according to the French-American-British (FAB) classification). In patients with RA, RDW was showed weak inverse correlation with both hemoglobin concentration (Hb) ($r_s = -0.37$, $P = 0.0035$) and mean corpuscular hemoglobin concentration (MCHC) ($r_s = -0.36$, $P = 0.0047$). On the other hand, RDW was showed weak correlation with the number of ringed sideroblasts in bone marrow ($r_s = 0.31$, $P = 0.023$). The increased RDW (≥15.0%) was associated with shorter overall survival (OS) ($P = 0.0086$). In patients with refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-t), effect of RDW on OS was less evident. These results suggested that increased RDW might reflect dyserythropoiesis, associated with deregulated hemoglobin synthesis and iron metabolism in MDS. Furthermore, increased RDW may have potential to be a prognostic significance in RA.

1. Introduction

Myelodysplastic syndrome (MDS) encompasses clonal hematologic diseases characterized by ineffective hematopoiesis and peripheral cytopenia accompanied with morphologic dysplasia, and MDS diagnosis is achieved with universally adopted criteria [1]. Although morphologic dysplasia accompanied with cytopenia characterizes the dyshematopoiesis underlying MDS, their significance in the pathophysiology and prognosis of MDS remains controversial. Morphological abnormalities of blood cells were excluded from all prognostic indices including the International Prognostic Scoring System (IPSS) [2], the World Health Organization (WHO) Prognostic Scoring System (WPSS) [3], and the revised IPSS (IPSS-R) [4].

Genotypic alterations (i.e., clonal hematopoiesis) are evidently the main mechanism underlying hematopoietic defects in MDS.

In a recent study, red cell distribution width (RDW) was reported as an independent predictor of the post-test likelihood of an MDS diagnosis in patients with unexplained cytopenias [5].

RDW, which can be easily determined with an automatic blood cell counter, can improve the detection of morphological changes in red blood cells and further our understanding of their contribution to dyserythropoiesis in MDS. Moreover, RDW can afford a more objective approach to detect morphological changes compared with microscopy-based methods. Studies investigating RDW in MDS in detail are limited. Therefore, we investigated correlations between RDW and laboratory data associated erythropoiesis at diagnosis and subsequent clinical outcomes in patients with MDS for each subtype.

2. Materials and methods

2.1. Patients and clinical variables

In this retrospective study, a total of 101 newly diagnosed MDS patients who were diagnosed at our hospital between 2008 and 2016 were included. Diagnosis in all patients was achieved according to the 2008 WHO classification of myeloid neoplasms and acute leukemia [6]. Furthermore, all patients were reclassified according to the French-American-British (FAB) classification [7]. All patients underwent blood and bone marrow evaluations before treatment. Complete blood counts including RDW were measured by the fully automated XN-1000

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hematology analyzer system (Sysmex).

We investigated the laboratory data on peripheral blood and bone marrow and the clinical outcomes among in patients with refractory anemia (RA) or refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-t), according to the FAB classification. Chromosome subtypes were classified based on the MDS cytogenetic scoring system [8], which was used for IPSS-R [4]; very good (-Y, del (11q)), good(normal, del(5q), del(12p), del(20q), double including del (5q)), intermediate (del(7q), +8, +19, i(17q), any other single or double independent clones), poor (−7. inv(3)/t(3q)/del(3q), double including −7/del(7q), complex 3 abnormalities), very poor (complex > 3 abnormalities).

This study was approved by Institutional Review Board of Showa University.

2.2. Statistical analysis

Correlations of clinical variables in patients with RA or RAEB and RAEB-t were analyzed with Spearman's rank correlation coefficient (r_s).

Comparisons of RDW between very good or good prognosis chromosomal abnormalities and intermediate, poor, or very poor prognosis chromosomal abnormalities according to MDS cytogenetic scoring system were analyzed by Mann–Whitney *U* test in patients with RA or RAEB and RAEB-t.

The cutoff scores of RDW for prognosis were determined based on receiver operating characteristic (ROC) curve analysis. The sensitivity, specificity, and the area under the curve (AUC) were calculated. The ROC curves graphically displayed the trade-off between sensitivity and specificity. The cutoff scores were calculated for Youden Index method.

Probability of overall survival (OS) was estimated using the Kaplan–Meier method, and groups were compared using the log-rank test. Univariate survival analysis was conducted using Cox proportional hazard model. Since this study was aimed at exploratory to assess whether RDW was enough to evaluate as a prognostic factor, the sample size was not preset. A P value of < 0.05 was considered as statistically significant. All statistical analyses were performed with JMP 13 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Patient characteristics were summarized in Table 1. The study cohort included the following MDS types according to the 2008 WHO classification: refractory cytopenia of unilineage dysplasia (RCUD, $n = 30$), RA with ring sideroblasts (RARS, $n = 8$), refractory cytopenia with multilineage dysplasia (RCMD, $n = 24$), RAEB-1 ($n = 21$), RAEB-2 ($n = 13$), MDS unclassified (MDS-U, $n = 4$), and MDS with isolated del (5q) ($n = 1$). According to the FAB classification, the study cohort included 59, 8, 30, and 4 patients diagnosed with RA, RARS, RAEB, and RAEB-t, respectively. Median patient age was 75 (range, 23–96) years, and median OS was 612 (range, 44–3240) days.

Azacitidine was administered to 24 patients, including 9 patients with RA and 15 patients with RAEB or RAEB-t. Lenalidomide was administered to five patients, including one patient with RA and four patients with RAEB. Immunosuppressive therapy, which was administered to 7 patients with RA. Erythropoietin was administered to 10 patients, including 9 patients with RA and 1 patient with RAEB. Combination chemotherapy was administered to 11 patients, including 1 patient with RA and 10 patients with RAEB or RAEB-t. Finally, allogeneic stem cell transplantation was performed in 10 patients, including 1 patient with RA and 9 patients with RAEB or RAEB-t.

3.2. Correlations between RDW and clinical variables

Correlations between RDW and clinical variables were shown in Table 2.

Table 1
Patient characteristics.

	n
Age (years)	
< 65	24
≥65	77
Sex	
Male	58
Female	43
Diagnosis according to WHO 2008 classification	
RCUD	30
RARS	8
RCMD	24
RAEB-1	21
RAEB-2	13
MDS-U	4
MDS with isolated del(5q)	1
Diagnosis according to the FAB classification	
RA	59
RARS	8
RAEB	30
RAEB-t	4
CMML	0

WHO, the World Health Organization: RCUD, refractory cytopenia of unilineage dysplasia: RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, refractory anemia with excess blasts; MDS-U, myelodysplastic syndrome, unclassified; FAB, the French-American-British; RA, refractory anemia; RAEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia.

Table 2
Correlations between red cell distribution width and clinical variables in patients with myelodysplastic syndrome.

	Patients with RA (FAB) $n = 59$		Patients with RAEB or RAEB-t (FAB) $n = 34$	
	Correlation coefficient	*P* value	Correlation coefficient	*P* value
Hb	−0.37	0.0035	−0.34	0.047
MCV	−0.028	0.83	−0.28	0.11
MCH	−0.17	0.20	−0.34	0.049
MCHC	−0.36	0.0047	−0.45	0.0083
Reticulocyte count	0.16	0.23	0.058	0.75
Serum iron	0.10	0.46	−0.18	0.33
Serum ferritin	0.17	0.23	0.091	0.63
Number of ringed sideroblasts in bone marrow	0.31	0.023	0.24	0.20

RA, refractory anemia; FAB, the French-American-British; RAEB, refractory anemia with excess blasts; RAEB-t, RAEB in transformation; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

In patients with RA, weak inverse correlation was found between RDW and Hb ($r_s = -0.37$, $P = 0.0035$), MCHC ($r_s = -0.36$, $P = 0.0047$). Weak correlation was also found between RDW and the number of ringed sideroblasts in bone marrow ($r_s = 0.31$, $P = 0.023$).

In patients with RAEB and RAEB-t, we found inverse correlation between RDW and MCHC ($r_s = -0.45$, $P = 0.0083$). Moreover, we found weak inverse correlation between RDW and Hb ($r_s = -0.34$, $P = 0.047$), MCH ($r_s = -0.34$, $P = 0.049$).

3.3. Comparison of RDW and chromosomal subtypes

We compared RDW between very good or good prognosis chromosomal abnormalities and intermediate, poor, or very poor prognosis chromosomal abnormalities according to MDS cytogenetic scoring system.