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Research Article

RDW is a Novel Prognostic Parameter in Diffuse Large B Cell Lymphoma in the Rituximab Era

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Abstract

After the invention of rituximab, RCHOP became the standard regimen for Diffuse Large B cell lymphomas (DLBCL). Some patients still have a poor prognosis. Recent researches on Non-Hodgkin lymphoma has been related with prognostic biomarkers. Elevated RDW is accepted as a worse prognostic factor in some situations and diseases but the prognostic value has not been studied in DLBCL. The aim of this study was to investigate the prognostic role of RDW in DLBCL.

Clinical and laboratory data from 217 DLBCL patients were retrospectively studied in a single center by multivariate analysis, Kaplan-Meier survival analysis, forward stepwise and Cox regression analysis were used to examine the effect of RDW on survival.

In this data set, elevated RDW levels were strongly associated with shorter survival. RDW was determined as a predictor of mortality and seems to be a simple, cost-effective novel prognostic parameter in DLBCL in the rituximab era.

Keywords: Erythrocytes; Chemotherapy; Lymphoma; RDW; Prognostic; Biomarker

Introduction

Diffuse Large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin's lymphoma. Although the addition of rituximab has improved survival, some patients are still refractory to standard therapy. To better identify patients at high risk for poor prognosis, a number of conventional parameters have been defined. The age of patient, gender, clinical stage, beta-2 microglobulin level, serum albumin level, IPI score, LDH, are well known factors [1,2]. Several ongoing studies are evaluating the prognostic role of new parameters in DLBCL such as CRP, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), absolute lymphocyte count (ALC) and Ki-67. These novel parameters have been defined recently for predicting the response to therapy and survival [3-8]. Recent studies have shown that red cell distribution width (RDW) has been reported as a prognostic marker in various situations such as cardiovascular diseases, kidney diseases, critically ill patients and some cancers such as lung cancer, breast cancer and multiple myeloma [9-16]. On the other hand the importance of RDW is lacking in DLBCL. The aim of this study was to determine the association between RDW and survival in DLBCL.

Materials and Methods

A retrospective analysis was made of data from patients between 2006 and 2014 treated in a in a tertiary hematology and oncology center. All patients were diagnosed with DLBCL and treated with R-CHOP therapy in a single institute. Totally two hundred and sixty four patients were recorded. Patients with serious heart disease, severe renal insufficiency, HIV infection, unresolved hepatitis B or C infection, prior chemotherapy, steroid administration in the previous 15 days and secondary cancers were excluded. Eighteen of the patients have hepatitis B or hepatitis C infection, 12 have renal insufficiency, 8 have serious heart disease, 9 of the patients has secondary malignancy then they excluded. Known associations with a worse prognosis, including some of the primary extranodal lymphomas such as testicular, central nervous system, breast and primary mediastinal lymphoma patients were also excluded [17,18]. Remaining of 217 patient files were reviewed and age, sex RDW, hemoglobin, LDH, clinical stage and IPI scores were recorded at the time of diagnosis. The study was approved by the Local Ethics Committee.

Statistical analysis

Chemotherapy response was assessed after three or four courses of R-CHOP by CT, MR or PET/CT according to the initial radiological imaging methods. To determine overall survival and progression free survival Kaplan-Meier method and two-tailed log-rank test were used. Progression free survival was calculated from diagnosis until the date of relapse, progression or last follow-up. Overall survival was calculated from initial diagnosis until the date of death by any cause or date of the last follow-up. The selection of an objective cut-off value of RDW for survival analysis was identified using receiver operating characteristics (ROC) curve analysis and was used when analyzing the RDW as dichotomized variables into alive versus death (Figure 1). The most sensitive and specific cutoff value of RDW for survival was 15.5 mg/dl, with an AUC value of 0.65 (95 % confidence interval [CI], 0573-0.726, p= 0.000, Figure-1) according to the ROC curve analysis. Data were analysed using the SPSS version 15.0. A value of $p<0.05$ was accepted as statistically significant.

Results

The median age at diagnosis was 60 years (range, 21-90 years). Male to female sex ratio was similar. Median follow-up period was 21.9 months (range 3.2-108 months) for all and 26.1 months for surviving patients. Overall, 57 deaths were recorded. The 1 year and 3 year overall survival rates were 79.6 % and 62.5% respectively. Primary nodal lymphoma was determined in 55% of patients and remaining extranodal involvement/primary extranodal disease was in 45%. The characteristics of the patients are listed according to the cut off value of RDW 15.5 in Table 1.

Table 1. Baseline characteristics in RDW high and low groups.

	RDW ≤15.5		RDW >15.5		p-value
	N	%	N	%	
Age	59.7(21-90)		60.3(22-87)		0.871
Gender (M/F)					
Female	66	59.4	45	40.6	
Male	52	49.0	54	51.0	0.124
LDH IU/L	446 (135-3800)		598 (37-4874)		**0.021**
Extranodal involvement	118	54.3	99	45.7	**0.004**
Stage I-II	61	57.5	45	42.5	
Stage III-IV	57	51.3	54	48.7	0.360
IPI Low	66	60.5	43	39.5	
IPI Intermedİate	28	50.0	28	50.0	
IPI High Intermediate	17	42.5	23	57.5	
IPI High	7	58.3	5		0.216

The mean age, gender, stage were similar in both RDW high and low groups although extranodal involvement and LDH were different. To further figure out the prognostic role of RDW, multivariate Cox regression analysis was performed. Several factors were associated with worse outcome including RDW were shown in Table II.

Table 2. Multivariate analyses for progression free survival cox proportional hazards model (Forward Stepwise).

	PFS		
	HR	95% CI	P
RDW	1.155	1.053-1.266	**0.002**
Age	1.022	1.001-1.044	**0.044**
LDH	-	-	0.461
Hemoglobin	-	-	0.267

In multivariate analysis, RDW, LDH, hemoglobin and age showed close association with worse outcome. The results of multivariate analysis indicated that RDW was an independent prognostic factor for survival (HR, 1.155; 95% CI, 1.053-1.266; p=0.002; Table III). Age, RDW and LDH were also shown to be independent prognostic factor for OS and age and RDW was for PFS.

Table 3. Multivariate analyses for overall survival cox proportional hazards model (Forward Stepwise).

	OS		
	HR	95% CI	P
RDW	1.091	1.005-1.183	**0.037**
Age	1.030	1.012-1.047	**0.010**
LDH	1.005	1.003-1.007	**0.016**
Hemoglobin	-	-	0.191

Discussion

Although there have been many studies about the significance of hematological parameters, such as lymphocyte/monocyte ratio, lymphocyte, hemoglobin, neutrophil/lymphocyte [6, 7, 19, 20] there has been no study regarding RDW in lymphoma. The current study showed that higher RDW levels at diagnosis indicated a worse prognosis in DLBCL in the rituximab era. Patients with higher RDW levels were correlated with shorter progression-free survival (Figure 2) and shorter overall survival compared to the normal RDW group (Figure 3). The precise mechanism between RDW and lymphoma prognosis is unknown, but potential mechanisms might be related with the inflammatory condition. A number of cytokines such as TNF-alfa, IL-6 induce inflammation in cancer patients. IL-6 also found to be related to RDW and RDW was found to be a significant independent predictor for mortality [21]. The role of inflammation in cancer pathogenesis has been emphasized in many trials. Cytokines cause DNA damage through the activation of signaling pathways such as NK-kB and STAT3, stimulate cell proliferation and reduce apoptosis [22]. Several cause and effect relationships has been defined such as endometriosis and endometrium cancer [23] , chronic gastritis (H.pylori) and gastric cancer [24], chronic hepatitis and hepatocellular carcinoma [25], barrett's esophagitis and esophageal cancer [26]. Inflammation affects erythroid progenitor cells and leads to increased RDW by shortening the life of red blood cells [27]. Oxidative stress may also contribute to anisocytosis [28]. In NHANNES III study, the relationship of RDW with mortality could not be explained by inflammation alone, because when evaluated according to the CRP level, which is the best indicator of chronic inflammation, a relationship was still remained between RDW and mortality in the low CRP group. This confirms that RDW is an independent prognostic factor in inflammation [29].

RDW reflects the heterogeneity of the erythrocytes and higher RDW values show increased variation of erythrocyte volumes (anisocytosis) and increased RDW levels could be associated with some diseases. RDW and mortality with increasing age has been well defined in different trials [30]. In the data of the current study, RDW remained a significant predictive biomarker for OS and PFS even after adjustment for age in multivariate analysis. In a study by Patel et al, it was reported that RDW predicted mortality in older adults who did not have anaemia [31]. When the other nutritional deficiencies are excluded, RDW remains significant for mortality. Similarly in the current study, patients were assessed according to hemoglobin levels in univariate analysis and multivariate analysis for RDW but it has not affected the result. Patel et al grouped patients according to nutritional deficiencies. Iron, folate and B12 levels were found to have a significant correlation with RDW but it was understood that they did not change the effect of RDW on mortality. Furthermore, it was thought that the removal of the deficiency with folate supplements in those with folate deficiency would cause a drop in RDW but following supplementation, the RDW-mortality relationship continued [31]. According to the evidence, high RDW may be an indicator not only of nutritional deficiency in the hemopoietic system but also of a disturbance involving several systems. Anemia is also commonly observed in cancer patients and may cause alterations with RDW levels.

Despite the increasing data for the prognostic role of RDW there have been only few studies in specific cancer types. Seretis et al showed the activity of RDW in invasive breast cancer and showed that higher RDW levels were correlated with unfavorable prognostic factors [13]. Warwick et al reported that higher RDW levels before thoracic surgery showed higher mortality and shorter survival [32]. In another study in lung cancer patients, an association was shown between RDW and stage or survival [33]. Survival analysis of the study is strong in PFS (p=0,002) however not very strong in OS (p=0,037).

Currently, Nccn-IPI score is the valid and most preferred tool for risk classification of lymphoma. While we were searching the effect of RDW on survival we didn't add the IPI score because no significant correlation were observed in univariate analysis and some components of the IPI were already included into the calculation in multivariate analysis. RDW has the required properties of a good biomarker, such as ease of application, repeatability and low cost. RDW is an inexpensive test, so is worth always reporting to the physician as it could be a risk assessment tool in further studies [14]. However RDW may be integrated in the IPI scoring system alone or with other hematological parameters proven to be correlated with survival [34, 35]. Further studies are needed.

There are several limitations in the current study; (1) RDW level was only examined at the time of diagnosis and was not checked again. A single measurement may be influenced by various factors. (2) The median follow up is relatively short. Because the count of patients were more in recent years. 3) CRP, albumin or other markers could be investigated to correlate with RDW. They were not available in most of the patients on time of diagnosis. (4) Most of the patients are low or low-intermediate IPI score. (5) Pathological results were

not enough detailed. Germinal zone and non-germinal zone DLBCL was not defined for all patients. The strengths of the study are; (1) The study was designed only among DLBCL patients. Other non-Hodgkin lymphoma subtypes were not included to avoid heterogeneity. (2) All the patients were treated with R-CHOP only because different regimens may influence survival. (3) All measures were performed in the same automated modern laboratory.

In conclusion despite the limitations, to our knowledge this is the first study to determine the prognostic value of RDW in DLBC lymphomas. Longer prospective studies are required to validate the importance of RDW as simple prognostic marker in DLBCL. However higher RDW levels at diagnosis in DLBCL patients seems to be associated with poor prognosis according to our findings, so we believe it could be a new prognostic marker. Although the underlying mechanism has not yet been identified, it is a simple and cost-effective tool which may be used in clinical oncology practice or it may also be incorporated into the IPI scoring system.

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Conflict of interests

No conflict of interests

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