ORIGINAL ARTICLE

RED CELL DISTRIBUTION WIDTH (RDW) AS A MARKER OF DISEASE ACTIVITY IN PATIENTS WITH HAIRY CELL LEUKEMIA

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Summary: Red cell distribution width (RDW) was examined in 18 patients with hairy cell leukemia (HCL) treated with 2-chlorodeoxyadenosine (2-CdA), in 5 patients treated with Interferon alpha (IFN-alpha) and in 9 patients subjected to splenectomy. Out of 18 patients treated with 2-CdA one patient was excluded of the study because of association of HCL with acquired sideroblastic anemia. In the remaining 17 patients the mean value of RDW before terapy was 18,8% (range 13,5% to 25,0%) and dropped after successful theapy after 6 to 12 months to the mean value of 13,6% (range 11,2% to 17,9%) and after 18 months to 13,4% (range 12,6% to 14,7%) ($p = 0,00015$ and $p = 0,00049$ respectivelly). The hemoglobin level increased from the mean value of 119 g/l (range 99g/l to 157 g/l) before therapy to the mean value of 145,9 g/l (range 127 g/l to 172 g/l) after 6 to 12 months and after 18 months to 147,8 g/l (range 132 g/l to 168 g/l) ($p = 0,000017$ and $p = 0,00036$ respectively). The same trend was observed in the group of patients treated with IFN-alfa. The RDW decreased from the mean value of 21,3% (range 18,8% to 28,7%) to the mean value of 15,3% (range 12,4% to 16,7%), ($p = 0,031$). The hemoglobin level increased in this group of patients from the mean value of 115 g/l (range 98 g/l to 127 g/l) to the mean value of 136 g/l (range 127 g/l to 146 g/l) ($p=0,031$). In 9 patients in complete hematologic remission 34 to 293 months after splenectomy the mean value of RDW was 13,9% (range 13,0% to 15,5%). Conclusion: Increased RDW in HCL is associated with active disease and is reversible after successful therapy. This phenomenon has not been reported in the literature yet. Preliminary results show that the increase of RDW may be due to the dyserythropoiesis.

Key words: *HCL; RDW; Dyserythropoiesis*

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Introduction

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder characterized by abnormal mononuclear cells of B lymphocyte origin infiltrating bone marrow and spleen. Patients often present with some combination of anemia, neutropenia, thrombocytopenia and splenomegaly (1,6,11). Anemia is very common and is observed in 75 to 80 percent of patients (3,9,12). The mechanism of anemia has been attributed to the splenic sequestration with a substantial increase in splenic volume (13) and to the reduced red-cell production due to a diffuse bone marrow infiltration by tumor cells and bone marrow fibrosis (4,15). Erythrokinetic studies revield that in addition to splenic sequestration and reduced red-cell production there is some reduction in red cell-survival (5). The anemia is usually normocytic or macrocytic with slight anisocytosis and poikilocytosis. The mean cell volume (MCV) is nearly always toward the upper limit of normal and often elevated (6). We have observed that red cell distribution width, which is indicative of anisocytosis, reflects in HCL the diseases activity (7).

Patients and Methods

The RDW values were assessed in 32 patients with HCL divided in three groups according to the therapy.

The diagnosis of HCL was based on the presence of morphologically characteristic cells in the peripheral blood and/or in the bone marrow, demonstration of the tartarat resistant acid phosphatase activity in the neoplastic cells (16), typical histologic pattern in bone marrow biopsies with infiltration by malignant cells characteristically surrounded by a rim of pale cytoplasm resulting in clearly separated nuclei (4). In all splenectomized patients the diagnosis was reconfirmed by the histologic finding in the spleen showing heavy infiltration of the red pulp by abnor-

mal interdigitating mononuclear cells and the presence of blood-filled spaces lined by hairy cells, so called pseudosinuses (14).

Response criteria to the therapy

Complete hematologic remission (CR) required all of the following:

1) Complete absence of hairy cells in the peripheral blood.
2) Normalization of peripheral blood counts (hemoglobin level ≥120 g/l, white cell count ≥$3x10^9$/l, absolute neutrophil count ≥$1,5x10^9$/l, platelet count ≥$100x10^9$/l, disappearance of retroperitoneal lymphadenopathy and hepatosplenomegaly by CT or US scan.

Partial remission (PR) required

1) Failure of normalization in one of low peripheral blood counts.
2) Reduction grater than 50% of lymphadenopathy and/or hepatosplenomegaly. The Red Cell Width (RDW in %) was determined using Coulter JT3 or Coulter STKS. Normal value 11,5-14,5%.

Patients

Group 1 (see table 1): consisted of 18 patients treated by 2-chlorodeoxyadenosine (2-CdA). All patients received a single cycle of 2-CdA at a dose of 0,1 mg/kg/d by continous intravenous infusion for 7 days. Out of 18 patients there were 14 male and 4 female with an age range 39 to 82 years (median, 61,5 years). 11 patients were previously treated: 7 by splenectomy, 2 by splenectomy and IFN-alpha, 2 by repeated course of IFN-alpha because of relapse, in remaining 7 patients the 2-CdA therapy was the first treatment. All 18 patients responded to the therapy, in 16 complete hematologic remission was achieved, in one patient (M.W. No 11) the remission was partial because the platelet count increased after therapy only to $90x10^9$/l, but the hemoglobin level after therapy was within normal limits. Patient V.J. (No 15) reached the normal hemoglobin level after 18 months. Patient V.M. (No 6) was excluded from further assessement because of associated acquired sideroblastic anemia and will be considered separately.

Group 2 (see table 2) consisted of 5 patients treated by Interpheron-alpha. 3 patients were previously treated by splenectomy, 1 patient received the second course of IFN-alpha because of relapse. Out of 5 patients there were 4 male and 1 female with an age range of 39 to 78 years (median, 58 years).

Group 3 (see table 3) consisted of 9 patients treated by splenectomy with the follow up period after splenectomy between 34 and 293 months (median, 193 months). Out of 9 patients there were 5 male and 4 female with an age range between 51 to 71 years (median, 60 years). Bone marrow biopsy revieled interstitial infiltration by hairy cells in all patients. All patients have been after splenectomy in complete hematologic remission.

Table 1: Hemoglobin levels and RDW in Patiens with hairy cell leukemia treated with 2-chlorodeoxyadenosine

				Before therapy		6 to 12 months after therapy		18 months after therapy	
	Name	Age/Sex	Previous therapy	RDW (%)	Hb (g/l)	RDW (%)	Hb (g/l)	RDW (%)	Hb (g/l)
1.	T.D.	58/F	SPL	23,5	99	14,6	155	14,7	132
2.	K.Z.	61/F	SPL	14,3	119	13,0	127	-	-
3.	Z.J.	43/M	-	22,5	104	12,6	155	12,4	148
4.	D.S.	72/M	-	15,9	122	13,5	162	13,2	163
5.	M.L.	66/F	SPL	23,6	82	14,8	144	14,7	140
6.	V.M.*	71/M	SPL	21,3	130	24,0	133	24,3	79*
7.	Š.V.	82/F	-	18,6	106	13,2	131	13,0	135
8.	M.O.	76/M	SPL, INF	13,5	108	13,0	151	13,1	155
9.	L.Z.	43/M	SPL	15,2	129	13,9	143	13,7	147
10.	F.J.	71/M	-	19,3	107	13,5	149	-	-
11.	M.W.	54/M	-	22,6	104	13,4	172	14,1	168
12.	B.J.	49/M	IFN (2x)	14,2	100	12,6	160	12,8	153
13.	A.M.	39/M	SPL	14,4	157	13,3	163	12,8	160
14.	Z.S.	51/M	-	23,5	107	17,3	144	14,7	150
15.	V.J.	62/M	SPL, INF (2x)	19,4	134	17,9	114	13,7	153
16.	K.A.	68/M	SPL	15,4	137	12,9	145	-	-
17,	F.J.	59/M	-	19,3	110	13,5	132	12,6	137
18.	Ž.J.	74/M	IFN (2x)	25,0	111	13,6	155	14,2	133
			Mean	18,8	119	13,6	145,9	13,4	147,8

SPL - splenectomy
IFN - interferon-alpha
* - patient excluded of the study

Table 2: RDW and hemoglobin levels in patients with hairy cell leukemia treated with IFN-alpha

				Before therapy		After 6 months	
	Name	Age/Sex	Previous therapy	RDW (%)	Hb (g/l)	RDW (%)	Hb (g/l)
1.	O.M.	76/M	SPL	19,2	121	15,5	127
2.	J.S.	66/M	IFN-alpha	18,8	127	16,7	127
3.	M.H.	39/M	SPL	19,2	116	15,6	146
4.	D.T.	58/F	SPL	20,7	98	16,7	141
5.	J.B.	49/M	-	28,7	111	12,4	138
			Mean	21,3	115	15,3	136

SPL - splenectomy
IFN - alpha-interferon-alpha

Table 3: Hemoglobin levels and RDW in patiens with hairy cell leukemia trated by splenectomy

	Name	Age/Sex	Previous therapy	After splenectomy (months)	Bone marrow biopsy	Lymph nodes	RDW (%)	Hb (g/l)
1.	D.R.	71/F	SPL	293	INT	0	13,7	158
2.	V.J.	63/M	SPL	214	INT	0	13	146
3.	B.V.	68/F	SPL	194	INT	0	13	130
4.	K.J.	60/M	SPL	194	INT	0	14,2	173
5.	H.J.	51/M	SPL	193	INT	0	14	150
6.	V.J.	54/M	SPL	181	INT	0	15,5	177
7.	V.J.	51/F	SPL	173	INT	0	13,6	129
8.	V.J.	62/M	SPL	84	INT	0	13,1	159
9.	V.J.	53/F	SPL	34	INT	0	15,1	135
					Mean		13,9	150

SPL - splenectomy
INT - interstitial infiltration

Statistical analysis:

For the statistical analysis of RDW and hemoglobin concentration procedures described in (10) were used. As we have two measurements on the same individual at different times two statistical tests were used. In the case when normality of differences could be accepted (by means of D'Agostino skewness, kurtosis and omnibus normality tes-

ts) paired t-test was selected. If the assumption of normality was not valid Wilcoxon signed rank test was used.

In the first set of the data (17 and 14 subjects) when the result are compared after 6-12 months period and more than 18 months respectively it is again possible to reject the null hypothesis and accept the alternative one by means of Wilcoxon test. Values of RDW decreased significantly after the period of 6-12 month (p=0,00015) and after more than 18 months (p=0,00049).

In the case of Hb concentration it is possible to accept the null hypothesis as far as the normality of the differences is concerned and a paired t-test can be used. It allows to accept the alternative hypothesis and state that this variable increases x (p=0,000017 and p=0,00036 respectively).

It is not possible to verify the normality of the differences in the second set (data from 5 subjects) and Wilcoxon test allows to reject null hypothesis at 5% significance level. Therefore we can accept the alternative hypothesis which states that RDW is lower (p=0,031) and Hb concentration is higher after the treatment (p=0,031).

Results

Group 1 (see table 1): Out of 17 assessed patients the RDW values before therapy were increased in 13 patients, within normal limits in 4 patients with a range between 13,5 to 25,0% (mean, 18,8%). After 6 to 12 months of therapy the mean value of RDW was 13,6% (range 12,6 to 17,9%), (p=0,00015) it was normal in 14 patients, slightly above the upper limit of normal value in 3 patients (14,6%, 14,8%, 17,3%) and in the forth patient (V.J.,No 17: RDW 17,9%) the normal RDW 13,7% was reached after 18 months. The After 18 months RDW was within normal limits in 14 patients and only slightly above the upper limit of normal values in 3 (14,7%, 14,7%, 14,7%). The mean value of RDW after 18 months was 13,4% (range 12,4% to 14,7%), (p=0,00049).

The hemoglobin level simultaneously increased from the mean value of 119g/l (range 99 g/l to 157 g/l) before therapy to the mean value of 145,9 g/l (range 127 g/l to 172 g/l) after 6 to 12 months and to 147,8 g/l (range 132 g/l to 168 g/l) after 18months (p=0,00049 and p=0,00036 respectively).

Group 2 (see table 2): In the group of 5 patients treated with Interferon-alpha the RDW dropped from the mean value of 21,3% (range 18,8% to 28,7%) before therapy to the mean value of 15,3% (range 12,4% to 16,7%) after six months of therapy (p=0,031).

The hemoglobin level simultaneously increased from the main value of 115 g/l (range 98 g/l to 127 g/l) to the main value of 136 g/l (range 127 g/l to 146 g/l), (p= 0,031).

Group 3 (see table 3): In the group of 9 patients treated by splenectomy all patients were in complete hematologic remission. Mean value of RDW was 13,9%. The RDW was slightly above the upper limit of normal value in two patients (15,1% and 15,5%) despite normal levels of hemoglobin 135 g/l and 177 g/l respectively. The RDW values before splenectomy were not accessible. The examination before splenectomy was performed with an automated instrument not giving RDW value.

Discussion

Anisocytosis is an increase in the variability of erythrocyte size beyond that which is observed in a healthy subject. In automated instruments the calculated value of RDW reflects very accurately the degree of anisocytosis and makes the comparison of its changes possible. RDW has been found to be increased in iron deficiency anemia, megaloblastic anemias, congenital and acquired dyserythropoietic anemias (1,2,16,17). We have found that increased RDW in HCL was present in patients with an active disease and subsided after successful therapy with 2-CdA or IFN-alpha with a simultaneous rise of the hemoglobin levels. This phenomenon as far as we know has not been reported in the literature yet. Preliminary data show that the increased RDW may be due to the dyserythropoiesis (8). This finding is the subject of a further study and will be reported separately in more details.

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