ORIGINAL ARTICLE

LONG-TERM RESULTS IN HAIRY CELL LEUKEMIA TREATED WITH 2-CHLORODEOXYADENOSINE

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Summary: We treated 19 patients with hairy cell leukemia (HCL) with 2-chlorodeoxyadenosine. 15 patients followed up at least 6 months were evaluated. The follow up period varied between 6 months and 37 months (median, 19 months). 8 patients were previously treated. The overall response in 15 evaluable HCL patients was 100 %, with 87 % complete hematological remissions including three patients with retroperitoneal and mediastinal lymphadenopathy and one patient with leukemic infiltrates of the cornea; 13 % of patients achieved partial hematological remission. Soluble interleukin - 2 receptor (sIL-2R) considered as a reliable non-invasive marker of HCL tumor burden dropped from the median of 1350 pM/ml (range 188 to 9000 pM/ml) to the median of 84,3 pM/ml (range 37 to 382 pM/ml) RdW which reflects the anisocytosis of red cells decreased after therapy from the median of 20,6 % (range 13,1 - 25,0 %) to the median of 13,7 % (range 12,4 - 16,3 %).

Key words: *HCL; Therapy with chlorodeoxyadenosine; Long-term results; sIL-2R; RdW*

Hairy cell leukemia is a chronic lymphoproliferative disorder characterized by abnormal mononuclear cells of B lymphocyte origin infiltrating bone marrow and spleen. Patients, usually middle-aged men, often present with some combination of anemia, neutropenia, thrombocytopenia and splenomegoly. There is currently no single antibody which identifies an antigen unique to the hairy cells. These cells mostly demonstrate the pan-B-cells antigens Ig+, CD 19+, CD 20+, CD 22+, and usually lack surface CD 5- and CD 21-. Recently DBA 44, the hairy cell associated monoclonal antibody, has been used for demonstration of hairy cell in biopsy sections. Hairy cells characteristically express the receptor for interleukin-2 (IL-2R) on their membrane and although sIL-2R production is not unique only to hairy cells, the serum levels can be used as a marker of leukemic cell burden at diagnosis and for monitoring therapeutic efficiency, and for the detection of minimal residual disease (1,4,17).

Although the disease is relatively indolent, the majority of patients require treatment for life-treatening pancytopenia or symptomatic splenomegaly. Slenectomy has been used for over three decades as the initial treatment option for HCL. Splenectomy has been certainly beneficial for some patients (3) resulting in a significant improvement of their pancytopenia but splenectomy has no effect on bone marrow infiltration by leukemic cells. As a result, approximately 50 % of splenectomized patients have recurrent cytopenias that require systemic therapy. Interferon-alpha was the first drug in which de possibility to cure HCL was originally considered. This expectance was not fulfilled. Interferon-alpha was highly effective in the management of HCL but it did not have a curative potential. Relapses were observed wihin the 6^{th} and 28^{th} month after the with drawal of the therapy with interferon alpha. The introduction of two new purine analogues, 2-deoxycoformycin (DCF) and 2-chlorodeoxyadenosine (2-CdA) has dramatically improved treatment option in the last years (16). 2-CdA has been shown to induce complete remission (CR) in the majority of patients, with only a single cycle and a paucity of toxicities (7,16). However, persistence of minimal residual disease in the bone marrow, detected either by immunohistochemistry or polymerase chain reaction suggests that some patients are at risk of relapse (6, 10). The purpose of this study is to determine the durability of remissions and relapse rate in patients with HCL treated with a single cycle of 2CdA.

Patients and Methods

Since 1994 when 2-CdA became available in this country we have administered 2-CdA in 19 patients with HCL.

The diagnosis of HCL was based on the presence of morphologically characteristic cells in the peripheral blood and/or the bone marrow, demonstration of tartarate resistant acid phosphatase activity in the neoplastic cells (20), typical histologic pattern in bone marrow biopsies with infiltration of malignant cells characteristically surrounded by a rim of pale cytoplasm resulting in clearly separated nuclei (2). In all 6 splenectomized patients the diagnosis of HCL has been reconfirmed by the histologic finding in the spleen showing heavy infiltration of the red pulp by abnormal interdigitating mononuclear cells and the presence of blood-filled spaces lined by hairy cells, so called pseudosinuses (15).

The levels of sIL-2R were determined by a sandwich enzyme immunoassay (Immunoenzymometric assay Test Kit cat. 0559, IMMUNOTECH) normal values obtained by determination of sIL-2R in 20 healthy blood donors were 30,4 ± 13,6 pM/l.

The RdW (in %) was determined by Coulter JT3.

Table 1: Patient Characteristics

Characteristics	
No of Patients	15
Age (yr)	
Median	61
Range	43-84
Sex	
Male	12
Female	3
Previous treatment	
None	7
Splenectomy	4
IFN-alpha	2
IFN-alpha, SPL	1
IFN-alpha, SPL, IFN-alpha	1
Duration of HCL before therapy (months)	2CdA
Median	13
Range	1-137
Bone marrow infiltration	
Diffuse	10
Interstitial to diffuse	2
Interstitial	3
Hgb (g/l)	
Median	107
Range	(88-149)
ACN ($x10^9$/l)	
Median	0,7
Range	(0,4-7,7)
Platelets ($x10^9$/l)	
Median	92
Range	(35-218)

SPL, splenectomy; ACN, absolute neutrophil count

The main patient characteristics are listed in table 1. Out of 19 patients 15 with follow up period more than 6 months were avaluated. There were 12 men and 3 women, with an age range of 43 to 84 years (median, 61 years). Seven patients were previously untreated. Eight patients were previously treated, four with splenectomy, two with interferon-alpha (IFN-alpha) only, one with splenectomy then IFN-alpha and one with IFN-alpha then splenectomy followed by IFN-alpha and then 2-CdA. The duration of HCL befor the start of 2-CdA therapy varied between 1 and 137 months. The bone marrow biopsy performed before the administration of 2-CdA revieled diffuse infiltration in 10 patients, interstitial with some areas of diffuse infiltration in 2 and interstitial infiltration in 3 patients. The hemoglobin levels were 88 to 149 g/l (median, 107 g/l) absolute neutrophil counts 0,4 to 7,7 x 10^9/l (median, 0,7 x 10^9/l), platelet counts 35 to 218 x 10^9/l (median, 92 x 10^9/l).

Eligibility

Eligibility criteria included the following:

(1) Confirmed diagnosis of HCL based on the criteria mentioned above (2) follow up at least six months, (3) evidence of active disease, including any of the following: neutropenia (absolute neutrophil count < 1,5 x 10^9/l), anemia (hemoglobin level < 120 g/l), thrombocytopenia (platelet count < 100 x 10^9/l), retroperitoneal lymphadenopathy.

Administration of 2-CdA

All patients received a single cycle of 2-CdA (Leustatin, Cladribine, Orthobiotech, Raritan, NY) at a dose of 0,1 mg/kg/d by continuous intravenous infusion for 7 days.

Supportive care

Neutropenic patients who developed fever greater than 38 °C were given broad-spectrum antibiotics. However many such patients with sterile blood cultures had no evidence of infection. Packed red blood cells were not routinely transfused, but rather were administered only for symptomatic anemia. Platelets were administered prophylactically if the platelet count was less than 10 to 15 x 10^9/l. Hematopoetic growth factors were administered in only 4 patients with severe neutropenia.

Initial evaluation

At the time of study entry, all patients had a complete history and physical examination; complete blood cell count (CBC) with differential and platelet count; computed tomographic (CT) or ultrasound (US) scans of the chest, abdomen, and pelvis; marrow aspirate and unilateral bone core biopsy.

Patients were monitored without other therapy and were then reevaluated at 3 and 6 months with a unilateral bone marrow aspirate and biopsy and CT or US scans of the abdomen and pelvis.

Response criteria

Patients were evaluated for response 6 months after the initiation of 2-CdA. CR (complete hematologic remission) 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 blood cell count > 3 x 10(/l, absolute neutrophil count > 1,5 x 10^9/l, platelet count > 100 x 10^9/l, disappearance of retroperitoneal lymphadenopathy and hepatosplenomegaly by CT or US scans.

A PR (partial remission) required all of the following:

(1) Failure of normalization in one of low peripheral blood counts

(2) Reduction of greater than 50 % in abnormal lymphadenopathy or hepatosplenomegaly.

Relaps was defined: as reappearance of hairy cells in the peripheral blood and decrease of blood cell count below the values required for CR; increase of lymphadenopathy and/or hepatosplenomegaly.

Results

Out of 15 assessable patients, 13 (87 %) achieved CR with a single cycle of 2-CdA; 2 (13 %) achieved PR. Therefore, the overall response rate with a single cycle was 100 %. Of the 2 patients achieving PR, the platelet count was 48 x 10^9/l in the first and 90 x 10^9/l in the second one (table 2). Retroperitoneal and mediastinal lymphadenopathy disappeared in all three patients in whom it was noticed before the initiation of 2-CdA therapy. In one patient with infiltrates of cornea these infiltrates disappeared as well as mediastinal and retroperitoneal lymphadenopathy which were present before the initiation of therapy with 2-CdA. No patient died and no patient relapsed during the follow up which varied between 6 and 37 months (median, 19 months).

Table 2: Blood cell counts in 15 patients with HCL before and after therapy with 2-CdA

No	Name	Sex	ANC (x10^9/l)		Hgb(g/l)		Platelets x10^9/l		Remission
			before	after	before	after	before	after	
1	Z.J	M	0,4	2,2	35	123	35	112	CR
2	L.Z	M	1,2	5,0	128	148	293	412	CR
3	T.D	F	1,4	2,6	102	139	218	344	CR
4	M.O	M	7,7	4,0	120	154	106	173	CR
5	B.J	M	1,3	7,0	130	159	110	268	CR
6	M.L	F	0,6	5,8	118	147	140	422	CR
7	Ž.J	M	0,4	2,9	88	161	92	185	CR
8	F.J	M	1,2	2,0	106	141	111	154	CR
9	Š.V	F	0,4	5,5	101	129	87	192	CR
10	D.S	M	0,6	3,6	132	152	89	182	CR
11	V.J.	M	1,6	9,6	60	128	190	178	CR
12	Z.S.	M	1,7	7,9	107	142	79	131	CR
13	G.A	M	0,7	3,3	88	125	25	48	PR
14	M.W	M	0,7	4,4	104	168	58	90	PR
15	H.M	M	0,7	3,0	149	161	217	359	CR
Median			0,7	4,0	107	147	92	183	

Vysvětlivky: ANC - absolute neutrophil count
CR - complete remission
PR - partial remission

The sIL-2R levels were increased in all patients before the initiation of the therapy with 2CdA in the range of 188 to 9000 pM/ml (median, 1350 pM/ml), they decreased after the therapy to 37 to 382 pM/ml (median, 84,3 pM/ml) -see fig. 1. The lowest value of sIL-2R before initiation of therapy was in a patient treated previously with IFN-alpha, splenectomy and the second course of IFN-alpha therapy. Complete normalization of sIL-2R level after therapy was reached only in 2 patients (34,7 and 30,7 pM/ml).

The RdW values were before the therapy between 13,1 % to 25,0 % (median, 20,6 %), after therapy between 12,4 and 16,3 % (median, 13,7 %). The value 16,3 % was in the patient who reached only the PR (see Fig. 2).

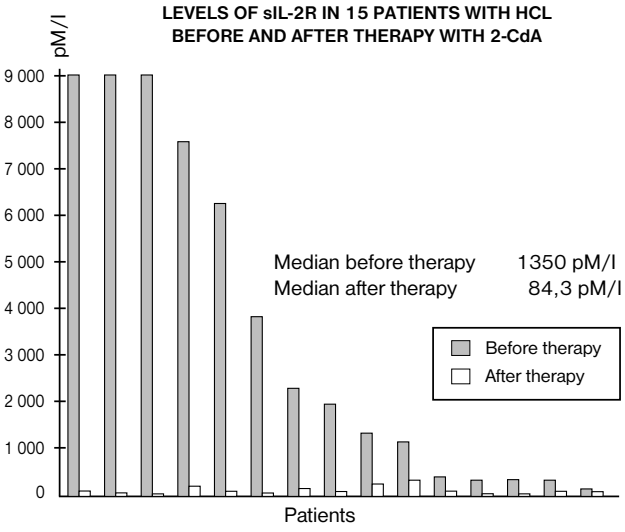

Fig. 1

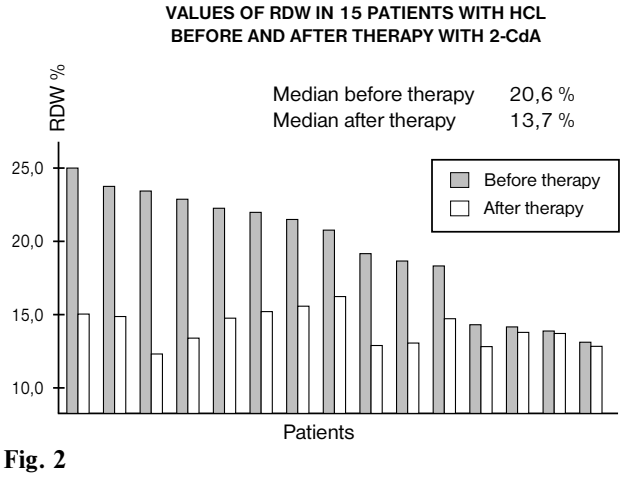

Fig. 2

Discussion

Our results confirm the effectiveness of 2-CdA in the treatment of HCL as reported also by other study groups (see Tab. 3). In 327 patients collected from 7 study groups com-

plete remission was achieved in 84 % of patients and partial remission in 14 %. Therefore, the overall response rate with a single cycle of 2-CdA therapy was 98 %. Mercieca et al (14) stressed differences in response in patients with and without abdominal lymphadenopaty. In 7 patients with abdominal lymphadenopathy he achieved complete remission only in 4 (57 %). Similar results, four CR and two PR were reported by Hakimian et al. (7). We concluded in our previous study that retroperitoneal lymphadenopathy is an unfavourable sign usually heralding the terminal stage of the disease (22). In this study complete remission was achieved in all three patients with retroperitoneal lymphadenopathy including one patient with leukemic infiltrates of the cornea on both eyes as reported previously (21). Assessment for response in HCL should not be performed to early, as responses found incomplete 1-3 months after therapy may turn to be complete responses when assessed later. More than 1 year may be needed before clearance of malignant cells from the bone marrow is complete (12). Response to 2-CdA seems to be unaffected by previous therapies (18). Increased sIL-2R levels which are considered as non-invasive marker of HCL burden dropped considerably after 2-CdA therapy to be mostly only slightly above the upper limit of normal values, but only in two patients they were within normal limits. This observation is in agreement with the opinion that complete eradication of tumoral cells may be very rare.

Tab. 3: Results of treatment in patients treated with 2 - CDA

Author	Number	treated: non-treat.	CR:	PR:	CR+PR	Failure
Merciece et al.[14]	23	18:5	20 (87%)	3 (13%)	23 (100%)	-
Tallman et al.[19]	50	13:39	40 (80%)	9 (18%)	49 (98%)	1 (2%)
Lauria et al.[13]	26	21:5	20 (77%)	6 (23%)	26 (100%)	-
Saven et al.[18]	143	74:69	123 (86%)	17 (12%)	140 (98%)	3 (2%)
Hoffman et al.[19]	48	27:21	42 (88%)	6 (12%)	48 (100%)	-
Filleul et al.[8]	22	12:10	17 (77%)	4 (18%)	21 (95%)	1 (5%)
Chrobák et al.	15	8:7	13 (87%)	2 (13%)	15 (100%)	-
Total	327	173:154 53%:47%	275 (84%)	42 (14%)	322 (98%)	5 (2%)

CR: complete remission, PR: partial remission

The RdW values reflecting the red cells anisocytosis were increased before the initiation of the therapy. This increased values were ascribed to the dyserythropoiesis and disappeared after successful therapy (5). Partial remission in one of our patients was associated only with a partial decrease of RdW from 20,6 to 16,3 %. In all the remaining patients almost normal values were achieved.

Whether the remission induced by 2-CdA may be considered as a cure is still unknown and is closely related to the discussion on eradication of malignant cells in complete responders. The present evidence suggests that residual disease persist in most if not in all complete remitters. Immunostaining of bone marrow biopsies with DBA 44 antibody in complete responders disclosed foci of malignant cells (6, 9).However, the persistence of residual disease is not necessarily predictive for relapse and only long-term follow up will settle this question. Data related to CR patients follow up are now available and suggest that relapses accumulate over time: median follow-up of 24, 13.5, 14, 23 and 19 months was associated with 22, 14, 7.6, 3.5, 14.2 and 0 relapse rate respectively (see table 4). The recognition that HCL may relapse or progress after responding to 2-CdA does not rule out the possibility that some remitters will enjoy indefinite remission which practically coincides with the cure. 2-CdA represents a major advance in the management of patients with HCL with an easy administration and long-term excellent quality of life that follows therapy with 2-CdA.

Tab. 4: Relapse of patients with HCL treated with 2-CDA

Author	No of pat.	Relapses		Median Folow-up	Folow-up (Months)	Relapse (Months)
		no	%			
Merciece et al.	23	5	22	25	6-30	6-17
Tallman et al.	50	7	14	24	12-44	CR: 12,24 (2x) 25, 35 PR: 6, 45
Lauria et al.	26	2	7,6	13,5	-	6, 12
Saven et al.	143	5	3,5	14	-	4-48
Hoffman et al.	48	5	10,4	-	-	-
Filleul et al.	22	3	14,2	23	-	28-37
Chrobák et al.	15	0	0	19	6-37	-
Total	327	27	8,2			

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