Supplementary material

Radzikowska E, Wakuliński J, Langfort R, et al. Cladribine treatment in patients with pulmonary Langerhans cell histiocytosis. Pol Arch Intern Med. 2023; 133: 16586. doi:10.20452/pamw.16586

Methods

Pulmonary function tests were performed by reference to the joint guidelines of the American Thoracic Society and the European Respiratory Society. Lung volume was measured via body plethysmography (MasterScreen software, ver. 4.65; Jeager, Wuerzburg, Germany) and the transfer factor of the lung for carbon monoxide (T_{LCO}) employing the single-breath technique [1,2]. The 6-min walk test (6MWT) was performed as recommended by the ATS [3].

At the beginning of the study 5(20%) patients were treated with higher dose of cladribine (0.15mg/kg of body weight), and 15 patients received cladribine at a dose of 0.12mg/kg of body weight.

Patients were considered to have a complete response (CR) if all signs and symptoms resolved (skin, symptomatic bone, and nodular lung lesions,); partial response non active disease (PR-NAD) - improvement in symptoms or signs; no new lesions; stabile NAD - endocrine dysfunction, neurodegeneration, unchanged lung cysts on high-resolution computed tomography with stable lung function parameters and asymptomatic radiological bone lesions were present. In other cases, they were classified with active disease (AD), which was subdivided into

regressive stable (persistence of symptoms or signs; no new lesions), or progressive (progression and/or development of new lesions) disease [4,5].

Adverse events were assessed using the Common Terminology Criteria for Adverse Events, ver. 5.0.

Statistical analysis

All statistical analyses were performed using Statistica software (ver.10.0; StatSoft, Tulsa, OK, USA). Shapiro-Wilk normality test was applied for assessment of distribution. The Student's t-test for dependent samples, and Wilcoxon test were applied. McNemar's test was employed to compare proportions. Overall survival (OS) was defined as time from start of treatment until death, progression, lung transplantation or last follow-up. Progression-free survival (PFS) was defined as the time from treatment until confirmed disease progression or death, whichever came first. Time-to-event analyses were conducted using Kaplan-Meier method.

All *P*-values are two-sided and was considered to reflect statistical significance of <0.05.

Material

Fourteen (70%) patients were chemo-naive, while 6 (30%) had received prior chemotherapy. Four (20%) patients had been treated with vinblastine, prednisone, and 6-mercaptopurine for 1 year; one with cyclophosphamide, doxorubicin, vincristine, and prednisone 4 courses, one with vinblastine, prednisone, and 6 mercaptopurine during childhood (for 1 year) and, 4 years later, with six courses of 2-CdA. In addition, one

male was treated with prednisone for 3 years, and 4 other patients with prednisone for 1 year. Two patients had been surgically treated to resect bone lesions, and one had thyroidectomy. In addition, one patient had received local injections of steroids.

Results

Table S1 Characteristics of patients treated with cladribine

All patients, n (%) Women Men	20 (100) 12 (60) 8 (40)
Age in years at the time of diagnosis, median (Q1; Q3)	36.5 (29-46.5)
Age in years at the time of cladribine treatment, median (Q1; Q3)	42 (32.5-47)
Smoking (pack/years), median (Q1; Q3) Ex-smokers, n (%) Smokers, n (%) Marijuana smoker, n (%)	10 (2.3-18.5) 17 (85) 3 (15) 5 (25)
Pneumothorax, number of patients (%) Pneumothorax before diagnosis, number of patients (%)	6 (30) 5 (25)
Time between first symptoms and diagnosis in months, median (Q1; Q3)	7 (3.5-30)
Observation time in months form diagnosis, median (Q1; Q3)	138 (83-186)
Observation time from the treatment initiation in months, median (Q1; Q3)	80 (38-110)

LCH localization, n (%)	
Lung	20 (100)
Diabetes insipidus	9 (45)
Bone	8 (40)
Skin	2 (10)
Sclerosing cholangitis	1 (5)
Liver, n (%)	1 (5)
Spleen, n (%)	1 (5)
Lymph nodes (abdominal), n (%)	3 (15)
Thyroid gland, n (%)	1 (5)
CNS, n (%)	4 (20)
Periaortic space, n (%)	1 (5)
MS LCH, n (%)	15 (75)
RO (−)	11 (55)
RO (+)	4 (20)
Isolated PLCH, n (%)	5 (25)
Concomitant diseases, n (%)	
Asthma	4 (20)
COPD	6 (30)
Obesity	8 (40)
Overweight	4 (20)
Arterial hypertension	9 (45)
GERD	13 (65)
Diabetes	5 (25)
Pancreatic cysts	1(5)
Varicose veins	1 (5)
Hypothyroidism	5 (25)
Hypercholesterolemia	8 (40)
Depression	2 (10)
Patients previously treated with Vinblastine and Prednisone, n (%)	4 (20)
Patients previously treated with steroids, n (%)	5 (25)

Patients previously treated with other chemotherapy [a], n (%)	1 (5)
Patients previously treated with cladribine, n (%)	1 (5)
Patients previously treated with surgery, n (%)	3 (15)
Clinical symptoms, n (%) Effort dyspnea Cough Sputum Sweats Weight loss Chest pain Bone pain Abdominal pain Polyuria and polydipsia Skin lesions	 16 (80) 15 (75) 8 (40) 5 (25) 6 (30) 7 (35) 8 (40) 1 (5) 9 (45) 2 (10)
HRCT, n (%) Cystic lesions Nodular lesions Sparing of the costophrenic angles Abdominal lymph nodes	 16 (80) 18 (90) 18 (90) 3 (15)
MRI of brain (number of patients with lesions), n (%)	4 (20)
MRI of pituitary gland (number of patients with lesions), n (%)	9 (45)
Echocardiography TVPG, mmHg, median (Q1; Q3) Ejection fraction, %, median (Q1; Q3)	 25.5 (24-27) 60 (58-67)

PLCH, Pulmonary Langerhans cell histiocytosis
RO, risk organs
TVPG, tricuspid valve regurgitation pressure

[a] Cyclophosphamide, doxorubicin, vincristine, prednisone
COPD, Chronic obstructive pulmonary disease
CNS, Central Nervous System
GERD, Gastro-esophageal reflux
HRCT, high resolution computed tomography
LCH, Langerhans cell histiocytosis
MRI, magnetic resonance imaging
MS-LCH, Multi system Langerhans cell histiocytosis

Table S2 Characteristics of patients treated with cladribine

No	Sex	Age at diagnosis	Age at the treatment	Smoking (pack/years)	Marijuana users	Extension	Involved organs	Pneumothorax (No of episodes)	COPD	GERD	Obesity	Overweight	AH	Diabetes	Hypothyroidisms	Asthma
1	m	18	28	2.5	1	MS-LCH	L,S	1		1	1					1
2	k	27	36	2		MS-LCH	L,P	5		1	1		1	1	1	
3	k	56	60	9		MS-LCH	L, P, brain, medistinum, Lymph		1	1		1	1	1	1	
4	m	26	32	4		MS-LCH	L,B,P				1					
5	k	46	46	20		IPLCH	L						1			1
6	k	5	19	0.25	1	MS-LCH	L,B,P, brain, Lymph	1								
7	k	38	39	4		MS-LCH	L,Liv,Sp,Lymph, SC	4		1						
8	m	47	48	60	1	IPLCH	L		1							
9	m	35	44	10		MS-LCH	L,P		1	1	1					
10	m	33	41	26		MS-LCH	L,B,		1	1	1					1
11	k	54	55	15		MS-LCH	L,B,		1	1	1		1	1	1	
12	k	31	33	10		IPLCH	L									
13	m	33	42	40		MS-LCH	L,B,	3	1							
14	m	23	23	0.5	1	MS-LCH	L,B,P,brain									
15	m	31	32	0.25		MS-LCH	L,B, S				1		1			
16	k	58	58	10		MS-LCH	L,B, P			1		1	1			
17	k	43	44	17		IPLCH	L			1		1	1			
18	k	39	42	0.25		MS-LCH	L,P,brain thyroid			1	1		1	1	1	
19	k	46	46	12		IPLCH	L			1						1
20	k	57	58	45	1	MS-LCH	L,B,P	1	1	1		1	1	1	1	

AH, arterial hypertension
B, bones
COPD, chronic obstructive pulmonary disease
CR-NAD, complete response-non active disease
GERD, gastro-esophageal reflux disease

IPLCH, isolated pulmonary Langerhans cell histiocytosis
L, lung
Liv, liver
Lymph, lymph nodes,
MS-LCH, multisystem Langerhans cell histiocytosis
P, pituitary gland
PR-NAD, partial response-non active disease
S, skin
S.C, sclerosing cholangitis
Sp, spleen

Table S3 Characteristics of patients treated with cladribine

No	Sex	Extension	Involved organs	Previous treatment	Dose od 2-CdA(mg/kg)	No. Of courses	Results after one year	Adverse Events (garde)	Death/ transplantation	Time from treatment to the last observation (months)	Time without progression (months)	Observation from diagnosis (months)
1	m	MS-LCH	L,S	PRE	0.15	6	CR-NAD	Infection(2)		115	115	218
2	k	MS-LCH	L,P	VBL+PRE	0.15	5	PR-NAD	Lymphopenia (2), Infection (2)	Death	43	43	144
3	k	MS-LCH	L, P, brain, medistinum, Lymph	VBL, PRE	0.12	4	PR-NAD	Leukopenia (3) Lymphopenia (3), Anemia (4), Thrombocytopenia(4), Infection(2)		120	120	156
4	m	MS-LCH	L,B,P		0.12	6	CR-NAD			110	110	196
5	k	IPLCH	L		0.12	6	CR-NAD			84	84	108
6	k	MS-LCH	L,B,P, brain, Lymph	VBL, PRE, 2-CdA, RTX, SURG	0.15	6	CR-NAD	Infection (2), Lymphopenia (2)		108	108	264
7	k	MS-LCH	L,Liv,,Sp,Lymph, SC	CHOP, VBL+PRE	0.15	6	CR-NAD	Infection (2), Lymphopenia (2,1)		129	129	144
8	m	IPLCH	L	PRE, VBL+PRE	0.15	6	CR-NAD	Infection (2), Lymphopenia (2)		110	110	120
9	m	MS-LCH	L,P		0.12	6	CR-NAD			111	111	228
10	m	MS-LCH	L,B,	Local steroids,	0.12	6	CR-NAD	Infection (3)		64	64	180
11	k	MS-LCH	L,B,	SURG	0.12	2	CR-NAD	Leukopenia (2), Lymphopenia (2), Thrombocytopenia (2)		64	64	96
12	k	IPLCH	L		0.12	5	CR-NAD	Leukopenia (2)		55	55	96
13	m	MS-LCH	L,B,	PRE, VBL+ PRE	0.12	4	Progression	Lymphopenia (2), Infection (3)	Transplantation	24	18	132
14	m	MS-LCH	L,B,P,brain		0.12	6	PR-NAD			28	28	40
15	m	MS-LCH	L,B, S	PRE	0.12	6	PR-NAD			29	34	52
16	k	MS-LCH	L,B, P		0.12	6	CR-NAD	Leukopenia (2), Lymphopenia (2),		32	34	144
17	k	IPLCH	L		0.12	6	CR-NAD	Leukopenia (2), Lymphopenia (2)		26	34	72
18	k	MS-LCH	L,P,brain thyroid	PRE, SURG	0.12	6	PR-NAD			34	34	192
19	k	IPLCH	L		0.12	6	CR-NAD			24	24	48
20	k	MS-LCH	L,B,P		0.12	6	Progression	Lymphopenia (2)	Transplantation	16	12	42

B, bones
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone
CR-NAD, complete response- non active disease
IPLCH, isolated pulmonary Langerhans cell histiocytosis
L, lung
Liv, liver
Lymph, lymph nodes,
MS-LCH, multisystem Langerhans cell histiocytosis
P, pituitary gland
PRE, prednisone

PR-NAD, partial response-non active disease
RTX, radiotherapy
S, skin
S.C, sclerosing cholangitis
Sp, spleen
SURG, surgery
VBL, vinblastine
2-CdA, cladribine

Competing interests

The authors declare no competing interests.

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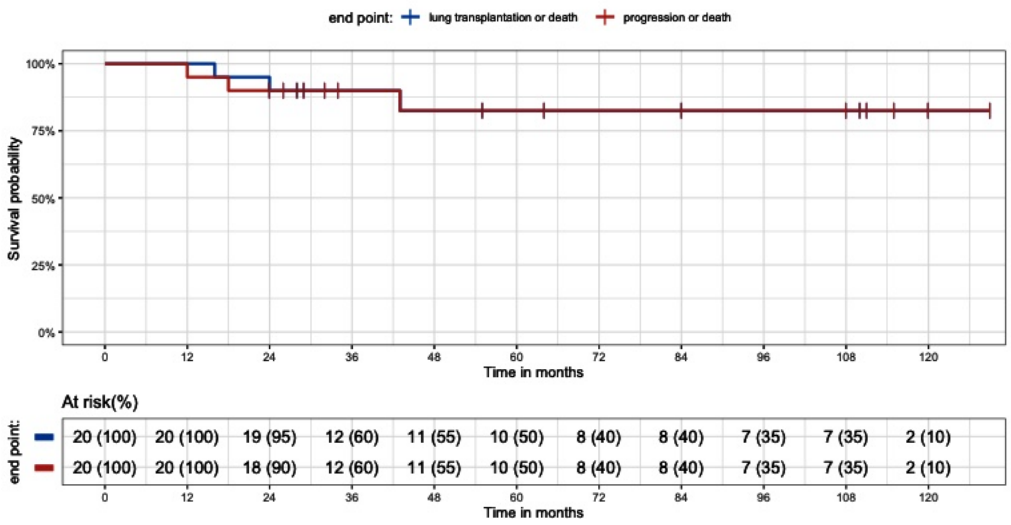
Figure S1 Kaplan -Meier analysis - time to progression, lung transplantation or death in patients with PLCH treated with cladribine


end point:
lung transplantation or death
progression or death
Survival probability
100%
75%
50%
25%
0%
0
12
24
36
48
60
72
84
96
108
120
Time in months
At risk(%)
end point:
20 (100) 20 (100) 19 (95) 12 (60) 11 (55) 10 (50) 8 (40) 8 (40) 7 (35) 7 (35) 2 (10)
20 (100) 20 (100) 18 (90) 12 (60) 11 (55) 10 (50) 8 (40) 8 (40) 7 (35) 7 (35) 2 (10)
0
12
24
36
48
60
72
84
96
108
120
Time in months