RESEARCH LETTER

Cladribine treatment in patients with pulmonary Langerhans cell histiocytosis

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Introduction Langerhans cell histiocytosis (LCH) is a rare disease of unknown etiology caused by clonal proliferation and infiltration of various organs by bone marrow–derived dendritic cells in the lymph nodes, bones, skin, lungs, pituitary gland, spleen, liver, and central nervous system (CNS).[1-3] The lungs may be involved as an isolated organ or as a part of a multisystem disease.

Pulmonary LCH (PLCH) can occur in patients of all ages but it is usually a disease of young, adult smokers, and no sex predilection is apparent.[1-3] In the lungs, Langerhans cells proliferate to form bronchiolocentric nodules, which may cavitate to form thick-walled confluent cysts with relative sparing of the costophrenic angles. PLCH progression may trigger fibrocystic lung destruction. Mutations in the *BRAF* (V600E), *MAP2K1*, *ARAF*, *NRAS*, and *KRAS* genes have been identified in more than two-thirds of PLCH cases, likely contributing to Langerhans cells proliferation.[1-3] The course of the disease is unpredictable. In some patients, smoking cessation induces regression, but in others the course may be aggressive.[2-5] Treatment strategies of adult-onset LCH are based on extrapolation of pediatric data, and on small retrospective studies.[1-10] At present, no standard treatment for adult PLCH is available.[2,3] Growing evidence suggests that cladribine (2-CdA) effectively cures PLCH, and a prospective clinical trial (www.clinicaltrials.gov, NCT01477397) is being conducted to verify this.[8-20] 2-CdA is a purine nucleoside analogue, which accumulates in the cells containing active deoxycytidine kinase, such as lymphocytes and dendritic cells. The principal indication for 2-CdA treatment is hairy cell leukemia.[1,2]

This work describes the results of a single-center observational study on 2-CdA treatment in adults with progressive PLCH.

Patients and methods From 2010 to 2021, 20 patients with histologically confirmed LCH were hospitalized in our department. All those who required chemotherapy (20 out of a total of 62 patients) received 2-CdA. Evaluation of the patients was performed according to the recommendations of the Histiocyte Society.[2,3]

2-CdA was administered intravenously at a dose of 0.15 or 0.12 mg/kg per day for 5 consecutive days at monthly intervals.

Data on patients' demographics, concomitant diseases, smoking status, clinical symptoms, organ involvement, pulmonary function tests (PFTs), and echocardiography were gathered. Lung and bone computed tomography (CT) scans, positron emission tomography, and magnetic resonance imaging (MRI) scans of the brain, pituitary gland, and abdomen were interpreted by experienced radiologists (KB, MJ, and JW). Pulmonary function improvement or deterioration were assessed in terms of changes in the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) exceeding 200 ml, or transfer factor of the lung for carbon monoxide (T_{LCO}) above 10% from baseline. PLCH stratification, evaluation of the disease status, and response to treatment, were based on the Histiocyte Society criteria.[2,3] The patients were assessed at the beginning of the treatment, before every course, at 3, 6, and 12 months after the treatment concluded, and annually thereafter. Further methodological details and information on statistical analysis of the results can be found in Supplementary material.

The study adhered to all relevant tenets of the Helsinki Declaration. All patients provided their written informed consent for the use of offlabel 2-CdA prior to the treatment, and approval for inclusion of each patient was given by

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TABLE 1 Pulmonary function tests in patients with pulmonary Langerhans cell histiocytosis; before, just after the treatment, and 1 year after the treatment

Parameter	Before treatment	Just after treatment	*P* value	1 year after treatment	*P* value
FVC, l, median (IQR)	3.2 (3–4.4)	3.34 (3–4.7)	0.48	3.47 (3–5.3)	0.04
FVC% pred, mean (SD)	89.95 (18.2)	90.7 (17.5)	0.46	95.2 (21)	0.03
FEV1, l, median (IQR)	2.18 (1.6–3.2)	2.3 (1.8–3.6)	0.01	2.21 (1.6–4.3)	0.048
FEV1% pred, mean (SD)	70.95 (21)	72.6 (20.6)	0.52	74.01 (28.7)	0.39
TLC, l, median (IQR)	6 (5.3–7.5)	5.8 (5.4–7.6)	0.85	5.73 (5.4–7.4)	0.5
TLC% pred, mean (SD)	107.75 (13.1)	109.5 (17.6)	0.87	109.8 (18.6)	0.98
Patients with TLC <80% pred, n (%)	2 (10)	0	–	1 (5)	–
Patients with TLC >120% pred, n (%)	5 (25)	4 (20)	1	3 (15)	0.48
RV, l, median (IQR)	2.2 (2–3.4)	2.43 (1.7–3)	0.12	2.38 (1.7–3.5)	0.01
RV% pred, median (IQR)	141 (113–213)	134 (104–175)	0.13	128 (102–173)	0.03
Patients with RV <80% pred, n (%)	1 (5)	1 (5)	–	1 (5)	–
Patients with RV >120% pred, n (%)	13 (65)	11 (55)	0.61	10 (50)	0.37
T_{LCO}, mmol/min/kPa, median (IQR)	4.44 (3.5–6.7)	4.8 (3.6–6.4)	0.27	4.72 (3.5–6.4)	0.04
T_{LCO}% pred, mean (SD)	54.1 (23)	55.36 (22)	0.23	56.5 (22)	0.02
6MWT distance, m, mean (SD)	525.65 (110.72)	526.83 (123.62)	0.97	534.17 (132.41)	0.79
PaO_2, mm Hg, mean (SD)	75.42 (10.69)	76.65 (8.79)	0.56	75.06 (9.65)	0.48
$PaCO_2$, mm Hg, median (IQR)	35 (32–37)	36 (33–37)	0.97	34 (26–37)	0.23

Abbreviations: 6MWT, 6-minute walking test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; PaO_2, partial pressure of oxygen in the blood; $PaCO_2$, partial pressure of carbon dioxide in the blood; pred, predicted; RV, residual volume; TLC, total lung capacity; T_{LCO}, transfer factor of the lung for carbon monoxide

our Institutional Board and Bioethics Committee (KB 11/2019).

Results Patient characteristics are listed in Supplementary material, *Tables S1–S3*. Twenty patients (12 women) at the median age of 42 (interquartile range [IQR], 19–60) years were treated with 2-CdA. All patients had a smoking history, and 5 (25%) declared marijuana use.

Five patients exhibited isolated PLCH, and 15 individuals (75%) showed involvement of the lungs and other organs, such as pituitary gland with diabetes insipidus (9 [45%]), bone (8 [40%]), CNS (4 [20%]), lymph nodes (3 [15%]), skin (2 [10%]), bile duct (1 [5%]), liver (1 [5%]), thyroid gland (1 [5%]), and periaortic space (1 [5%]).

Concomitant diseases were diagnosed in 18 patients (90%). Most frequently they were gastroesophageal reflux disease (65%), arterial hypertension (45%), obesity (40%), hypercholesterolemia (40%), chronic obstructive pulmonary disease (30%), asthma (20%), and overweight (20%).

Fourteen patients (70%) were chemonaive, while 6 (30%) had received prior chemotherapy, 5 (25%) had received prednisone, and 3 patients (15%) had undergone surgery.

The most frequently reported symptoms were exertional dyspnea (80%), cough (75%), polyuria and polydipsia (45%), expectoration of sputum (40%), and bone pain (40%). Characteristic cysts and nodules with sparing of the bases of both lungs were evident in 18 patients (90%), but 2 (10%) had nodules only. Additionally, in 5 individuals (25%) reticular lesions were present. Pneumothorax during the active phase of the disease was apparent in 6 patients (30%) (in 5 at the disease onset and in 1 at the time of progression).

The PFTs are listed in TABLE 1. Two patients evidenced hypoxic respiratory insufficiency. FEV1 below 70% of the predicted value (pred) was detected in 13 patients and FVC below 80% pred in 5 patients. Three participants exhibited FEV1/FVC ratio below 50%. Hyperinflation (residual volume >120% pred) was apparent in 13 cases (65%). Fourteen patients displayed T_{LCO} below 70% pred. On the 6-minute walking test, all patients walked the predicted distance, with desaturation below 89% evident in 4 of them (33%). A slight increase in arterial pulmonary pressure was present in 2 patients (10%).

Treatment One patient received 2, 2 patients 4, 2 patients 5, and 15 patients 6 courses of 2-CdA. The patients with bone lesions additionally received bisphosphonates. *Pneumocistis jiroveci* prophylaxis was administered in 10 patients.

Nineteen patients (95%) responded to 2-CdA treatment. Just after the treatment, complete regression (CR) (nonactive disease) and partial regression (PR) (nonactive disease) were noticed in 13 (65%) and 6 individuals (30%), respectively. One woman did not respond to 2-CdA. Additional data are presented in Supplementary material, *Table S3*.

At follow-up 1 year after the end of the treatment, 13 (65%), 5 (25%), and 2 patients (10%) were diagnosed with CR, PR nonactive disease, and progression, respectively. All bone lesions evidenced continuous resolution; CR was obtained

in 6 (30%) and PR in 2 (10%) of the patients. Significant regression of CNS lesions was noticed in 4 patients (20%), and no progression was found during follow-up. The spleen and skin lesions regressed completely. Sclerosing cholangitis was present on abdominal MRI examination and markedly improved during treatment. The observed changes were inactive, permanent consequences of the disease. CR of the enlarged lymph nodes was noticed. Chest high-resolution CT showed CR of the nodules and of small cavitated lesions in 13 cases (65%). Previously recurrent pneumothoraxes resolved completely. Stabilization of the number and volume of the cysts was observed in 14 participants (70%).

Two patients with progression of the lung lesions underwent successful lung transplantation.

Pulmonary function assessment At 1 year after termination of the treatment, significant increase in the median FVC (3.2 [3–4.4] vs 3.47 [3–5.3] l; $P = 0.04$), mean (SD) FVC% pred (89.95 [18.2] vs 95.2 [21]; $P = 0.03$), median FEV1 (2.18 [1.6–3.2] vs 2.21 [1.6–4.3] l; $P = 0.048$), median T_{LCO} (4.44 [3.5–6.7] vs 4.72 [3.5–6.4] mmol/min/kPa; $P = 0.04$), and mean (SD) T_{LCO}% pred (54.1 [23] vs 56.5 [22]; $P = 0.02$) were evident. In addition, a median percentage of predicted residual volume decreased after 2-CdA treatment (141 [113–213] vs 128 [102–173]; $P = 0.03$) (TABLE 1).

One year after the treatment a significant increase (>200 ml) in FVC and FEV1 was noticed in 8 (40%) and 7 patients (35%), respectively. Moreover, 4 participants (20%) displayed a 10% increase in T_{LCO}% pred.

In 2 patients, deterioration in the PFTs was noted. 2-CdA treatment did not improve pulmonary hypertension.

Adverse events The patients who had received prior chemotherapy experienced more frequent myelosuppressive events. Only in 1 chemonaive patient myelosuppression was the cause of premature termination of the treatment. However, the patient achieved CR, and after 8 years she is still in remission. Neutropenia and thrombocytopenia caused earlier treatment termination in 5 patients (25%). The most serious grade 4 events were thrombocytopenia and anemia in the oldest female patient, who had previously received chemotherapy. Treatment-related toxicities included leukopenia of grade 1, 2, and 3 in 3 (15%), 4 (20%), and 1 patient (5%), respectively; lymphopenia of grade 1, 2, and 3 in 3 (15%), 7 (35%), and 2 patients (10%), respectively; thrombocytopenia of grade 1, 2, and 4 in 2 (10%), 1 (5%), and 1 patient (5%), respectively; and anemia of grade 4 and 2 in 1 patient (5%) each. Upper respiratory tract infections of grade 2 were recorded in 7 (35%), and of grade 3 in 2 patients (10%). The infections occurred in the patients previously treated with steroids or chemotherapy. One patient with severe lung impairment, after 2 episodes of pneumothorax with pleurodesis, pretreated with oral steroids, developed pulmonary aspergilloma (after 4 courses of 2-CdA). Initially, the treatment resulted in PR, but then he developed progression in the lungs and was transplanted. Although a high proportion of our patients had gastrointestinal reflux disease, we recorded no gastrointestinal events; however, all these patients were taking proton pump inhibitors. Two patients previously treated with vinblastine showed grade 1 neuropathy prior to 2-CdA administration, but this did not deteriorate during the therapy.

Follow-up and survival analysis During follow-up (median, 80 [IQR, 20–132] months), an obese woman with pancreatic cysts developed acute pancreatitis 1 year after the treatment termination. She died suddenly of an unknown cause 2 years after the termination of the treatment with 2-CdA. Another obese man with severe obturation showed *P. jiroveci* pneumonia at 6 months after the treatment termination; however, he had not received prophylaxis. In addition, 1 year later, this patient developed acute respiratory distress syndrome during an influenza infection, despite having been vaccinated against influenza. Moreover, 1 woman developed chronic myelogenous leukemia 12 months after completion of 2-CdA treatment. Imatinib was introduced and remission has been achieved. The patient is still treated for leukemia.

Fast deterioration of pulmonary function with partial regression of bone and pituitary lesions was detected in 1 woman. This patient was then successfully transplanted.

All patients survived 1 year from the beginning of the study, and 5-year survival was achieved by 80% of the participants (Supplementary material, *Figure S1*).

Discussion In this study, 2-CdA was found an effective treatment for PLCH, improving or stabilizing not only skin, bone, liver, spleen, CNS, and lymph node lesions, but also pulmonary function, not just after the treatment termination but also 1 year later. 2-CdA was effective as both the first- and second-line treatment. The response rate was 95%, and during the time of observation, progression was noted in 2 patients (10%). PLCH is rare in adults, and no standard treatment exists. Based on the experience in children,[1-3] the previous protocol with vinblastine, prednisone, and mercaptopurine was withdrawn due to poor efficacy and a high number of adverse events.[1-5] Our unpublished data support this decision.

To date, a few reports on 2-CdA treatment of adult PLCH patients have appeared.[8-20] Saven and Burian[18] showed that 2-CdA benefited 12 patients, offering an overall response rate (ORR) of 75%. Half of the patients had PLCH; however, PFTs were not performed. 2-CdA improved pulmonary function in 4 out of 5 PLCH patients treated by Grobst et al.[14] Grau et al[13] noticed a 66% ORR in 9 patients treated with 2-CdA. Similar observations of 5 and 7 PLCH

patients provided with 2-CdA were published by Pardanani et al[16] and Adam et al,[17] respectively. Cantu et al[9] compared vinblastine, 2-CdA, and cytarabine in 58 PLCH patients with concomitant multifocal bone disease. Treatment failure or disease reactivation within 1 year after the treatment termination was recorded in 84% of the patients treated with vinblastine / prednisone, 59% of those given 2-CdA, and only 21% of those taking cytarabine (Ara-C). The authors concluded that Ara-C was the most effective treatment, being better than 2-CdA. Recently, Neel et al[19] presented the results of 2-CdA treatment in 23 adults with LCH: ORR rate was 91%, and CR was achieved in 50% of cases. Moreover, a pooled analysis of 48 additional cases revealed ORR in 88% and CR in 49% of the patients. During a 2- and 5-year observation, disease progression was seen in 20% and 30% of the patients, respectively.[19] Among 38 adult patients, 31 with multisystem LCH, treated with 2-CdA and presented by Goyal et al,[20] ORR was noticed in 79% and CR in 26%. Of the patients with PLCH, 60% showed improvement in T_{LCO}, while 30% had stable PFTs, and 2 patients progressed with their lung disease. The differences among patients who received 2-CdA in the front-line setting and later-line setting (ORR, 83% vs 67%; CR, 38% vs 17%; $P = 0.3$) did not reach statistical significance.[20] Recently, Cao et al[8] presented treatment outcomes of 266 new LCH adult cases (60% with PLCH, 18 patients with isolated PLCH), mainly treated with 2-CdA. The estimated 3-year overall survival and event-free survival rates were 94.4% and 54.7%, respectively, but the patients with lung involvement were not analyzed separately. In our group of patients, the number of those who achieved CR was slightly higher than in the other published case series (65% vs 20% to 50%). It was due to the presence of patients with isolated PLCH, who generally respond better to treatment. However, it should be underlined that it is difficult to assess the regression of pulmonary lesions. In the patients who display nodules, regression results in their CR, but in the case of cysts, there is no good assessment of the disease activity. The most sensitive assessment tools are PFTs. In the presented group, 45% of the patients experienced significant improvement in PFTs, and in 20% a significant increase in T_{LCO} was noticed. Only 1 patient who did not respond to 2-CdA displayed deterioration in PFTs.

Even though 2-CdA exhibits relatively high myelotoxicity, serious adverse events (grade 3–4) were noted in only 3 patients (15%), 2 of whom had been pretreated. The adverse event profiles of all other published patients were similar. Goyal et al[20] observed grade 3 adverse events in 4 out of 38 patients; 2 lymphopenia cases requiring dose delays, 1 febrile neutropenia, and 1 congestive cardiac failure. In the group presented by Neel et al,[19] 9 out of 23 patients developed grade 3–5 neutropenia and / or severe (grade 3–5) infection. Three patients died. Cantu et al[9] recorded cytopenia (grade 3–4) more frequently in the vinblastine than in the 2-CdA and the Ara-C groups (75%, 37%, and 20%, respectively). Moreover, the patients treated with vinblastine experience neuropathy. In our study, severe neuropathy was not observed in the patients pretreated with vinblastine.

Saven et al[18] reported 1 case of chronic myelomonocytic leukemia among 12 patients with LCH treated with 2-CdA, and Goyal et al[20] noticed 2 cases of leukemia among 38 LCH patients. In the presented group of patients, 1 woman had chronic myelogenous leukemia. She received imatinib and is currently in remission. Another our patient developed *P. jiroveci* pneumonia a few months after termination of 2-CdA treatment. Grobst et al[14] recommended sulfamethoxazole / trimethoprim and valaciclovir prophylaxis during 2-CdA treatment, and 6 months after the treatment cessation. We agree with this recommendation, and now in our center sulfamethoxazole / trimethoprim is prescribed to patients treated with 2-CdA.[1,2]

Our work had several limitations. First, this was a single-center observational study. However, all 20 patients who had indications for chemotherapy received 2-CdA, and underwent close observation following the same schedule. Second, the number of patients was small, and they represented a wide clinical spectrum, which reflects the fact that PLCH is a rare disease. Moreover, only a few patients with PLCH had progressive or refractory disease that required chemotherapy.

In addition, a genetic analysis of the mutations within the mitogen-activated protein kinase pathway was not presented. On the other hand, a correlation of the *BRAF* gene mutations with response to 2-CdA is inconclusive. Goyal et al[20] revealed that 2-CdA therapy was associated with a higher response rate in *BRAF*-V600E cases, as compared with *BRAF*-V600-wild type cases.[20] In the study of Cao et al,[8] *BRAF* deletion correlated with multisystem LCH, particularly with liver, pituitary, and thyroid involvement, but bone involvement was associated with the *BRAF*-V600E mutation.

A multicenter, prospective international trial is urgently needed to establish a standard treatment for adult PLCH.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

NOTE An online identifier was ascribed to ER (ORCiD ID, https://orcid.org/0000-0002-2585-8594).

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