

Results of Treatment with 2-Chlorodeoxyadenosine (2-CDA) in Multiple Reactivations or Refractory Langerhans Cell Histiocytosis

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Article information	Abstract
<p>Article history: Received: 21 Apr 2012 Accepted: 20 July 2012 Available online: 29 June 2013 ZJRMS 2014; 16(1): 94-97</p> <p>Keywords: Langerhans Cell Histiocytosis 2-Chlorodeoxyadenosine Children</p> <p>*Corresponding author at: Department of Pediatrics, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. E-mail: gh_miri@yahoo.com</p>	<p>Background: Langerhans cell histiocytosis (LCH) is the most common type of histiocytosis and characterized by abnormal proliferation and excess accumulation of inflammatory and langerhans cells at various tissue sites. Clinical manifestations are variable, ranging from spontaneously regressing single bone lesion to multisystem disease, life-threatening and refractory to treatment. Conventional chemotherapy has been shown to be effective in treatment of majority of patients with LCH. However, treatment of refractory disease or multiple reactivations is difficult. The aim of this study is to assess the efficacy of 2-CDA in relapsed or refractory LCH.</p> <p>Materials and methods: Four patients with relapsed or refractory LCH that were treated with 2-chlorodeoxyadenosin (2-CDA) enrolled in this study. All patients had received at least one prior chemotherapy regimen. The dose and schedule of 2-CDA was 6 mg/m²/day for 5 days every 3-4 weeks.</p> <p>Results: Median age at the time of treatment with 2-CDA was 9.7 years. Three patients had multisystem disease and one had multifocal bone lesions. All patients had multifocal bone lesions. None of them had risk organ involvement. Mean course of treatment with 2-CDA was 9.5. Radiologic evaluations revealed complete resolution of bone lesions in two (50%) patients. In one (25%) patient lesions regressed (partial response) and in another (25%) the disease remained stable. Drug related side effects were minimal. At the present time all patients are alive.</p> <p>Conclusion: Our study demonstrates that 2-CDA as a single agent is efficacious in treatment of multiple reactivations or refractory LCH and well-tolerated in children.</p> <p>Copyright © 2014 Zahedan University of Medical Sciences. All rights reserved.</p>

Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder, which is caused by clonal proliferation, accumulation of pathologic Langerhans cells and inflammatory cells, such as T cells, eosinophils, macrophages, and giant multinucleated cells in one or more organs [1]. Its etiology is unknown and the pathogenesis has not been clearly identified [2]. Although such a disorder usually affects children, it may occur at any age between neonatal period and adulthood and its clinical manifestations and prognosis are quite varied, depending on the site and extent of involvement [1, 3]. The disease is usually sporadic and non-hereditary, although some rare cases have been reported in twins and as familial clustering [4]. The diagnosis is based on the morphologic findings and identification of Birbeck granules (BG) using electron microscopy (EM) or positive staining for CD1a or S100 protein [5]. Treatment of patients with recurrent or refractory disease is known as a challenge. The use of 2-chlorodeoxyadenosine (2-CDA) produced satisfactory results in several studies carried out on these issues [6]. The published results of treatment using 2-CDA for children with the pertinent disease were obtained from the experiences of oncologists in other countries. In the present paper, we evaluated four

children with multiple reactivations or refractory histiocytosis, treated in Ali Asghar Children Subspecialty Hospital in Tehran using 2-CDA, in terms of rate of response and its side effects. The conventional chemotherapies and/or radiotherapy had no effect on them.

Materials and Methods

In this retrospective study, four children with the definitive diagnosis of refractory and/or multiple reactivations of LCH who had not respond to the conventional chemotherapy were selected. The criteria of selecting the patients were LCH definitive diagnosis and multiple reactivations or refractory to the current treatments. The definitive diagnosis of all the patients had been confirmed based on the histopathologic findings of bone biopsy and positive staining of immunohistochemistry (IHC) for CD1a antigen and S100 protein. Before starting treatment with 2-CDA, imaging studies, complete blood count (CBC) with differential, biochemistry, and evaluation of liver and renal function of the patients had been performed. After gaining written consents from the parents, the patients were treated with

2-CDA at a dose of 6 mg/m²/day for 5 consecutive days and intravenous infusion during 2 hours inside 100 ml of normal saline solution and repeated every 3-4 weeks. *Pneumocystis carinii* prophylaxis with cotrimoxazole had been prescribed for all the patients. Preceding to start each course of 2-CDA, physical examination, CBC with differential, biochemistry, and renal function tests had been performed.

Results

Tables 1 and 2 show the patient characteristics, before and after treatment by 2-CDA, respectively. All four patients were male. The median age of the patients at the time of diagnosis and at the time of treatment with 2-CDA were 23 months (range, 14-41 months) and 9.7 years (range, 5.5-18 years), respectively. Three patients had multisystem disease including multifocal bone involvement and one patient had only multifocal bone lesions without involvements of other organs. None of the patients had risk organ involvement (including liver, spleen, hematopoietic, and lungs). Two patients had diabetes insipidus (patients No. 2 and 4). The average period of the disease before treatment with 2-CDA was 92 months (range, 40-187 months). All the patients had received systemic chemotherapy. Two patients had records of receiving radiotherapy (patients No. 2 and 3). The four patients totally received 38 cycles of 2-CDA. The average number of the received courses was 9.5 (range, 6-13 courses). In addition to receiving 2-CDA, two patients (patients No. 1 and 4) received one and 6 courses of cytarabine 1 gr/m²/day within 5 days. Due to severe myelosuppression, fever and neutropenia,

cytarabine did not continue for patient No.1. Before starting the treatment with 2-CDA, the site of active disease in all the patients was bone. In general, for one patient (25%), lesions remained stable without any progression and/or a new lesion; for two patients (50%), the bone lesions were completely resolved in radiologic examination; for one patient (25%), lesions were regressed, but not completely (partial response). Generally, the overall survival and disease free survival were 100% and 50%, respectively.

With the average of 26-month follow-up period (range, 24-29 months) after treatment completion, all four patients are alive, without any symptom indicating any form of progression or new lesion. The hematologic toxicity caused by 2-CDA was negligible by itself and did not need treatment intervention. Fever and neutropenia periods were seen only in two patients who had received cytarabine simultaneously. No other drug-related side effects were found.

Discussion

Langerhans cell Histiocytosis is a clonal proliferative of Langerhans cells with variable biological behavior and clinical severity. This disease, previously known as Histiocytosis X, includes three clinical syndromes of eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease [7, 8]. The disease may manifest in a local or systematic manner. The clinical manifestations range from a single self-healing lytic bone lesion to a disseminating and life-threatening disease with several organs involvement.

Table 1. Patients' characteristics before treatment with 2-CDA

Patient No.	Sex	Age at diagnosis (mo)	Sites of involvement at diagnosis	No. of recurrence	Prior therapies
1	M	14	Bones	2, resistant to Tx in 2 nd relapse	Pred, VBL, MTX, 6-MP, VP16, CSA
2	M	24	Bones, skin	3	Pred, VBL, MTX, 6-MP, CPM, RT
3	M	14	Bones, exophthalmous	2	Pred, VBL, MTX, 6-MP, RT
4	M	41	Bone, skin	resistant to Tx at 1 st relapse	Pred, VBL, MTX, 6-MP

Abbreviations: M: male, DI: diabetes insipidus, Pred: prednisone, VBL: vinblastine, MTX: methotrexate, 6-MP:6-mercaptopurine, CPM: cyclophosphamide, CSA: cyclosporine A, VP16:etoposide, Ara-C:cytarabine; RT:radiotherapy, Tx: treatment

Table 2. Result of treatment with 2-CDA

Patient No.	Age at start of 2-CDA (mo)	Sites of involvement at start of 2-CDA	Dose of 2-CDA	No. 2-CDA courses	Concomitant drugs	Response to 2-CDA	Follow-up duration after last dose of 2-CDA (mo)	Patient Status At last visit
1	102	Bones	6mg/m ² /day	12	Ara-C	Stable disease	25	Alive, Without progression or new lesion
2	216	Bones, DI	6mg/m ² /day	7	None	Complete response	29	Alive, complete remission
3	67	Bones	6mg/m ² /day	6	None	Complete response	25	Alive, complete remission
4	81	Bones, skin, DI	6mg/m ² /day	13	Ara-C	Regression of lesions	24	Alive, Without progression or new lesion

The most common single involved location is bone. Every bone can be involved; however, the most common site is skull bone [1, 7]. Other sites that may be involved include skin, lungs, kidneys, spleen, lymph nodes, central nervous system (CNS) and bone marrow [9]. In 3-12% of cases with unifocal bone involvement cases, 11-25% of patients with multifocal bone lesions and 50-70% of cases with multisystem disease, reactivation of disease is seen in bone [10]. Although conventional first-line chemotherapy such as vinblastine, prednisone, mercaptopurine and etoposide is effective in LCH remission, treatment of the refractory and/or multiple reactivations disease may be difficult and its prognosis is poor [7, 11]. 2-CDA is an anti-metabolite and deoxyadenosine analogue, which has antiproliferative effect on lymphocytes and histiocytes and has toxic effect on monocytes through controlling synthesis of DNA [12]. This drug is used in treatment of chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML) in children, and hairy cell leukemia; its common side effects are limited to transient myelosuppression and T cells immunosuppression [13, 14]. After providing a complete response to the treatment with 2-CDA on three patients with refractory adults LCH by Saven et al., various studies were conducted on the usage of this drug for children and adults [15]. Several studies have shown that this drug can be effective in controlling refractory cases and/or LCH reactivation by itself [16, 17]. Saven et al. studied the activity of cladribine in adults LCH in which 58% were led to a complete response and 17% were led to partial response [17]. In the study carried out by Stine et al., the clinical response to 2-CDA in 9 out of 10 children with high risk LCH or with multiple reactivations was observed and toxicity caused by the drug was limited to bone marrow suppression [18]. In a study carried out by Weitzman et al., 62% of the patients with LCH without

risk organ involvement responded to the drug; in addition, response to treatment of the patients with low risk multisystem involvement and/or multifocal bone disease was higher than the patients with risk organ involvement [19]. In a study conducted by Carlos et al., 6 patients with recurrent LCH, who were treated by cladribine, were completely cured, there were a few hematologic toxicity, and no infectious complications were reported [14]. In addition, effectiveness of 2-CDA was demonstrated at CNS LCH [20]. In the present study, two patients were completely cured, one patient led to regression and the lesions remained stable in another patient. Two cases led to complete cure using only 2-CDA but one and six courses of cytarabine were also used at the same time for two other cases (patients No. 1 and 4). The results of treatment of our patients were similar to the ones of the other studies, whereas we had fewer patients. This study showed that single agent treatment using 2-CDA is effective in controlling multiple reactivation or refractory LCH and it is tolerated well by children. Although the conducted studies focused more on the refractory cases and/or multiple reactivations in the low risk group, conducting further studies on taking drug by newly diagnosed patients, cases with risk organ involvement, different time and doses of the drug is needed.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of interest

The authors declare no conflict of interest.

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References

- Weitzman S, Egeler RM. Langerhans cell histiocytosis: Update for the pediatrician. *Curr Opin Pediatr* 2008; 20(1): 23-29.
- Gasent Blesa JM, Pulla PM, Canales LJ and Candel AV. A review of Langerhans cell histiocytosis. *Cancer Therapy* 2008; 6: 935-44.
- McClain KL, Allen CE, John H. Histiocytic diseases. In: Pizzo Pa, Poplack DG, editors. *Principles and practice of pediatric oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011: 703-716.
- Arico M, Haupt R, Russoto VS, et al. Langerhans cell histiocytosis in two generations: A new family and review of the literature. *Med Pediatr Oncol* 2001; 36(2): 314-6.
- Abla O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: Current concept and treatments. *Cancer Treat Rev* 2010; 36(4): 354-9.
- Rodriguez-Galindo C, Jeng M, Khuu P, et al. Clofarabine in refractory Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2008; 51(5): 703-6.
- Azouz EM, Saigal G, Rudriguez MM and Podda A. Langerhans cell histiocytosis: Pathology, imaging and treatment of skeletal involvement. *Pediatr Radiol* 2005; 35(2): 103-15.
- Hoover KB, Rosenthal DI, Mankin H. Langerhans cell histiocytosis. *Skeletal Radiol* 2007; 36(2): 95-104.
- Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. *Hematol Oncol Clin North Am* 1998; 12(2): 247-58.
- Lau L, Stuurman K, Weitzman S. Skeletal Langerhans cell histiocytosis in children: Permanent consequences and health-related quality of life in long term survivors. *Pediatr Blood Cancer* 2008; 50(3): 607-12.
- Bernard F, Thomas C, Bertrand Y, et al. Multi-center pilot study of 2-chlorodeoxyadenosine and cytosine arabinoside combined Chemotherapy in refractory Langerhans cell histiocytosis with hematological dysfunction. *Eur J Cancer* 2005; 41(17): 2682-9.
- Saven A, Piro LD. 2-Chlorodeoxyadenosine: A potent antimetabolite with major activity in the treatment of indolent lymphoproliferative disorders. *Hematol Cell Ther* 1996; 38 suppl 2: 93-101.
- Biswas G, Khadwal A, Arora B, et al. Activity and toxicity of 2-CDA in Langerhans cell histiocytosis: A single institutional experience. *Indian J Cancer* 2007; 44(4): 137-141.

14. Rodriguez-Galindo C, Kelly P, Jeng M, et al. Treatment of children with Langerhans cell histiocytosis with 2-chlorodeoxyadenosine. *Am J Hematol* 2002; 69(3): 179-184.
15. Saven A, Figueroa ML, Piro LD, et al. 2-Chlorodeoxyadenosine to treat refractory histiocytosis X. *N Engl J Med* 1993; 329(10): 734-735.
16. Weitzman S, Wayne AS, Arceci R, et al. Nucleoside analogues in the therapy of Langerhans cell histiocytosis: a survey of members of the histiocyte society and review of the literature. *Med Pediatr Oncol* 1999; 33(5): 476-481.
17. Saven A, Burian C. Cladribine activity in adult langerhans-cell histiocytosis. *Blood* 1999; 93(12): 4125-30.
18. Stine KC, Saylor RL, Williams LL, et al. 2-Chlorodeoxyadenosine (2-CDA) for the treatment of refractory or recurrent Langerhans cell histiocytosis (LCH) in pediatric patients. *Med Pediatr Oncol* 1997; 29(4): 288-292.
19. Weitzman S, Braier J, Donadieu J, et al. 2-Chlorodeoxyadenosine (2-CDA) as a salvage therapy for Langerhans cell histiocytosis (LCH). Results of the LCH-S-98 protocol of the histiocyte society. *Pediatr Blood Cancer* 2009; 53(7): 1271-6.
20. Dhall G, Finlay JL, Dunkel IJ, et al. Analysis of outcome for patients with mass lesions of the central nervous system due to Langerhans cell histiocytosis treated with 2-chlorodeoxyadenosine. *Pediatr Blood Cancer* 2008; 50(1): 72-9.

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