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Single-agent cladribine as an effective front-line therapy for adults with Langerhans cell histiocytosis

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Langerhans cell histiocytosis (LCH) is the most common histiocytic neoplasm characterized by the activation of MAPK-pathway in most cases.[1] Most of the prospective studies in LCH are derived from pediatric population. Currently, there are no United States Food and Drug

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Authorship contribution

G.G., M.H. and J.P.A. collected the data. G.G. wrote the first manuscript draft with assistance from J.P.A. J.R.Y., T.G.C., C.C.H., A.P., D.J.I., R.V., K.L.R., J.H.R., C.J.D.-P., W.O.T., M.J.K., N.N.B., M.V.S. and R.S.G. critically revised the manuscript for important intellectual content; R.S.G. supervised the study; and all authors were involved in drafting the manuscript and approved the final version.

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Administration approved treatments for LCH. Prior studies have shown that cladribine presents an attractive option for LCH and related histiocytoses, due to its cytotoxic effect towards monocytes and monocyte-derived dendritic cells.[2–5] In a study of 13 adult LCH patients published two decades ago, cladribine demonstrated an overall response rate (ORR) of 75%.[3] However, FDG PET based assessment and *BRAF*-mutation information was not available in that era. A recent retrospective case series of 23 adults with relapsed/refractory LCH revealed an impressive ORR of 91% and did not include any patients treated in frontline with the drug.[6] There is a lack of contemporary studies examining the efficacy of cladribine in the front-line systemic treatment of adult LCH. Moreover, with the advent of targeted BRAF-inhibitors in histiocytic neoplasms, the role of cladribine in the context of *BRAF*-V600E mutation status is unknown. In this study, we report the efficacy of cladribine as frontline and subsequent therapy in adult LCH patients seen at a tertiary care institution.

After Institutional Review Board approval, we retrospectively reviewed the charts of all adult (≥18 years) LCH patients seen between January 1998 and December 2018. To minimize bias, each chart was reviewed by two investigators independently (G.G. and M.H.). Where necessary, the radiological images and histopathological slides were reviewed by an expert radiologist (J.R.Y.) and pathologists (K.L.R. and A.R.), respectively. *BRAF* V600E testing was performed by immunohistochemical studies (clone VE1, Abcam) or polymerase chain reaction (cobas 4800, Roche Molecular Diagnostics) on available formalin-fixed paraffin embedded tissue. We utilized the clinical documentation and radiological reports/images to assess the ORR based on the criteria described previously in prospective and retrospective adult histiocytosis studies.[7–11] We captured the best response, either clinical or radiological, depending on the organ involvement. Among patients with isolated skin involvement, response assessment was based on clinical examination. For patients with pulmonary LCH, pulmonary function test (PFT) reports were reviewed to capture change in diffusion capacity of carbon monoxide (DLCO). If there was some improvement, but not complete resolution of the symptoms or lesions attributed to LCH, it was categorized as a partial response (PR). The patients who had disease progression or no change in the disease status within three months of treatment initiation were categorized as progressive disease (PD). We used Kaplan Meier method to assess for progression-free survival (PFS) and overall survival (OS). All time to event analyses were conducted form the time of treatment initiation except for the duration of response, which was assessed from the time of best response.

We included 38 adult LCH patients in the study. The median age at cladribine initiation was 45 years (range, 23–78), and 51% were males. Although 31 (82%) patients had multi-system disease, all patients had more than one LCH lesion (multifocal). Most commonly involved organs were bone (65%), lung (60%), skin (38%), lymph nodes (30%), and pituitary/hypothalamus (27%). Cladribine was administered as frontline systemic therapy in 29 (76%) patients and as subsequent line treatment in 9 (24%) patients. Of the 9 patients who received cladribine in subsequent line, prior systemic therapies included vinblastine plus prednisone (with radiation) (n=1), prednisone (n=3), vinblastine (n=3), mycophenolate mofetil (n=1) and vemurafenib (n=1). Local therapies were previously utilized in 6 patients: surgery (n=3), radiation (n=2), and topical nitrogen mustard cream (n=1). Two patients received cladribine more than once during the course of their disease. The dosing of cladribine for all patients

was based on one of the two intravenous regimens (0.14 mg/kg for days 1–5 every 28 days or 5 mg/m^2 for days 1–5 every 28 days). Median number of cycles of cladribine administered was 4 (range, 1–9). Radiographic response assessment was conducted using 18F-Fluorodeoxyglucose (FDG) positron emission tomography computed tomography (PET/CT) in 17 (45%) patients and computed tomography (CT) or magnetic resonance imaging (MRI) in remaining 21 (55%) cases.

In our cohort, cladribine demonstrated an ORR of 79% (n=30), with 26% (n=10) complete responses (CRs) and 53% (n=20) PRs. Responses were seen in various disease sites: lung nodules/infiltrates (78%), bone (80%), lymph nodes (80%), skin (60%), and pituitary/hypothalamus (67%) (Supplementary Figure 1). Among patients who had pulmonary involvement, 60% had improvement in DLCO, while 30% had stable PFTs. Eight (21%) patients had PD- cystic/bullous lung disease (n=2), skin (n=2), abdominal/peritoneal lymph nodes (n=2), and hypothalamus (n=2). The response rates were similar among patients who received cladribine in the front line setting (ORR: 83%, CR: 38%) as compared to later line (ORR: 67%, CR: 17%, p=0.3). Grade 3 or above adverse events were seen in four patients: two lymphopenia requiring dose delays, one febrile neutropenia, and one congestive cardiac failure (deemed unrelated to cladribine). None of the patients received anti-infective prophylaxis for or developed pneumocystis jiroveci pneumonia. After initial disease response, progression was seen in three patients at median of 5 months (range 3 to 7). The median follow-up duration for the entire cohort was 6.3 years (95% CI; 4 to 10). Among the patients who responded to cladribine, 86%, 79%, 69% maintained their responses at years 1, 3, and 5, respectively. The 5-year PFS and OS for the entire cohort was 58% and 75%, respectively (Table 1, Figure 1). The 5-year PFS for patients who achieved a CR was comparable to those who achieved a PR (68% vs. 73%, p=0.8).

We attempted *BRAF-V600E* mutation testing on 30 (79%) available patient specimens. Of the 26 patients with successful testing, 12 (46%) were *BRAF*-V600E positive and 14 (54%) were *BRAF*-V600-wildtype (wt). Cladribine therapy was associated with higher ORR in *BRAF*-V600E cases as compared to BRAF-V600-wt cases, but this was not statistically significant (86% vs. 75%, p=0.48). The median PFS was not reached in *BRAF*-V600-wt patients compared with 2.6 years for *BRAF*-V600E mutated patients (p=0.26; Figure 1). At the time of last follow-up, 10 patients (26%) had died. Of those, cause of death was available on 9 patients: LCH (n=4), stroke (n=1), pulmonary embolism (n=1), gastrointestinal hemorrhage (n=1), and acute myeloid leukemia (AML; n=2). Of the 4 patients that died of progressive LCH, two had cystic pulmonary LCH causing respiratory failure, one developed sclerosing cholangitis unresponsive to cladribine and vemurafenib, and one died of progressive CNS disease. Among the two cases that died from AML, one had PD with cladribine subsequently achieving a CR using vinblastine and etoposide regimen. He developed chronic myelomonocytic leukemia (CMML) 4 years later, eventually transforming to AML. The second patient developed AML 7 years after being in CR from cladribine. The median survival from birth among those who died was 70.9 years (95%CI: 67–81).

In our study, cladribine monotherapy demonstrated a high ORR, with nearly two-third of the patients maintaining their responses at five year follow up. In a recent review of published

cases of cladribine treatment, the patients who had a PR were found to be at higher risk of relapse than those who had a CR.[6] However, our data did not reveal any differences in PFS based on the depth of response. Responses were seen irrespective of disease sites and *BRAF*-V600E status; however, there was a trend toward better PFS and OS in *BRAF*-V600-wt patients. Among patients with central diabetes insipidus from pituitary/hypothalamus involvement, the endocrinopathy and need for hormone replacement persisted despite radiographic improvement in disease as reported previously. Additionally, although cladribine was effective among patients with early (nodular) stages of pulmonary LCH, it did not achieve any response in advanced bullous cystic disease. However, previous reports have suggested that cladribine may be effective in cystic LCH as well,[12,13] and there is an ongoing clinical trial evaluating its role (NCT01473797).

Current systemic chemotherapy armemantarium for LCH includes cladribine, cytrabine, and vinblastine/prednisone. A retrospective study evaluating various chemotherapy regimens in bone LCH showed high treatment failure rate with cladribine (59%) and vinblastine/prednisone (87%) as compared with cytarabine (20%), suggesting the superiority of the latter drug.[2] In our study, however, responses were durable with cladribine in multi-system disease including osseou sites. Notably, the prior study included younger patients than our cohort and did not include multi-system LCH patients. These data may suggest a preferential role of cytarabine in bone only LCH or among pediatric patients who suffer from disease recurrence as adults. Although cladribine was associated with excellent efficacy in our cohort, a significant proportion (26%) of patients died, with majority of deaths unrelated to LCH. One patient died from sclerosing cholangitis, a dreaded complication of LCH that is difficult to treat. Notably, the patients who died were older than the overall cohort (median age 70 vs. 45 years) and had multiple comorbidities. Two patients also died from AML which has previously been reported to occur at high incidence in LCH patients.[7,14] Further studies are needed to ascertain the molecular underpinnings that lead to development of AML and possible correlations with new-onset morbidities in LCH surivors.

With the discovery of MAPK-pathway mutations in most LCH patients, targeted (BRAF- and MEK-) inhibitors offer an attractive treatment option with high response rates, which becomes especially important in refractory cases.[9–11] However, these drugs may necessitate indefinite treatment, as seen with vemurafenib in Erdheim-Chester disease, another MAPK-pathway driven histiocytic neoplasm.[15] Cladribine thus offers an attractive limited-duration treatment option with the potential for sustained remissions that avoids chronic toxicities that are associated with targeted agents. Our results suggest a trend toward improved outcomes using cladribine among *BRAF*-V600-wt patients; a finding that needs to be confirmed in future studies to optimize treatment selection based on molecular/genomic signature of the disease. Further studies are also needed to evaluate whether the effiacy of cladribine can be enhanced using targeted agents concurrently or sequentially.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict-of-interest Disclosures

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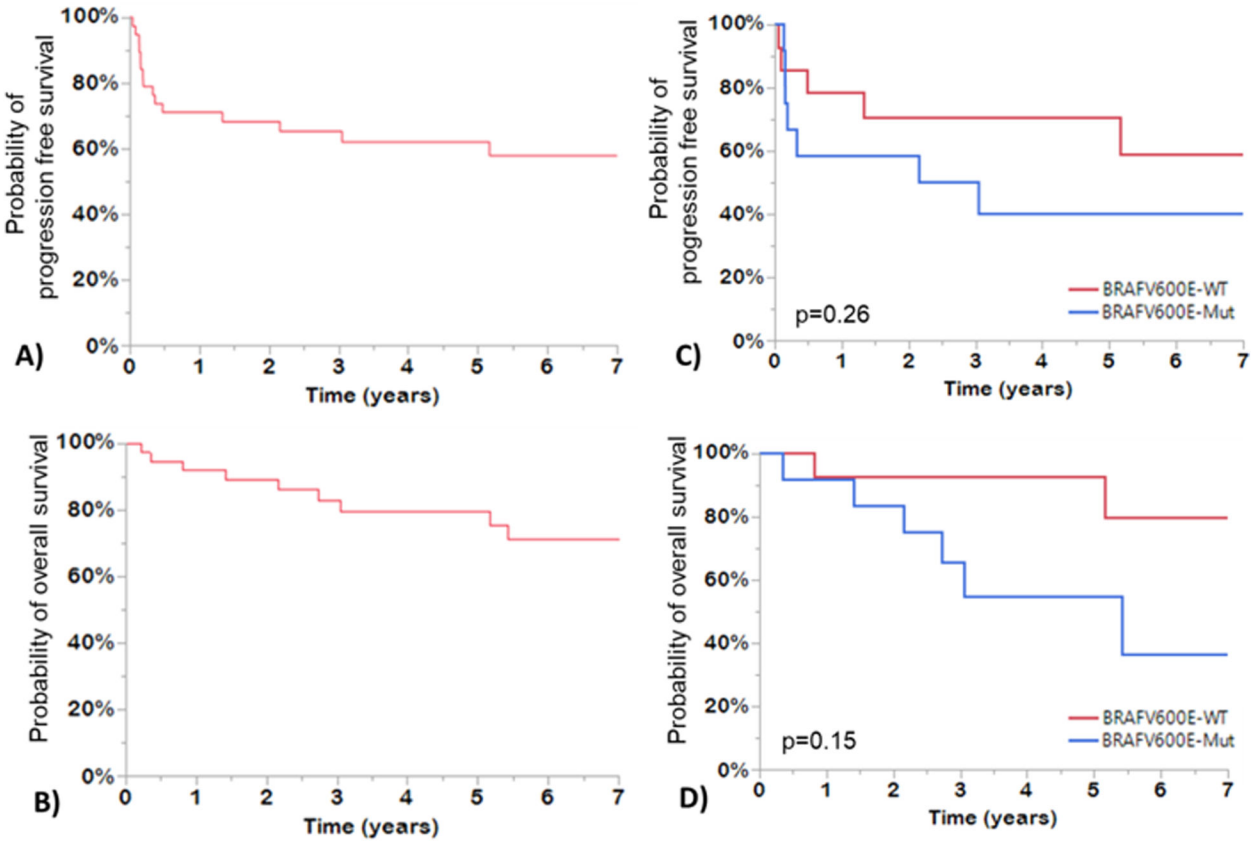

Figure 1.

Cladribine in adults with Langerhans cell histiocytosis. Progression free survival (A) and overall survival (B) for the entire cohort. Progression free survival (C) and overall survival (D) based on *BRAF*-V600E mutational status.

Table 1:

Outcomes of adult patients with Langerhans cell histiocytosis treated with cladribine

Parameter	Entire cohort (n=38)	Cladribine 1st line (n=29)	Cladribine subsequent line (n=9)
Response, n (%)	30 (79)	24 (83)	6 (67)
Complete response, n (%)	10 (26)	9 (31)	1 (11)
Partial response, n (%)	20 (53)	15 (52)	5 (56)
Progressive disease, n (%)	8 (21)	5 (17)	3 (33)
Overall survival			
Median, years (95% CI)	NR (11-NR)	5.4 (5-NR)	NR (0.8-NR)
1 year	89%	89%	88%
3 year	80%	76%	88%
5 year	75%	70%	88%
Patients progressed, n (%)	12 (32)	9 (31)	3 (33)
Progression free survival			
Median, years (95% CI)	NR (2-NR)	5 (1-NR)	NR (0.04-NR)
1 year	68%	68%	67%
3 year	62%	60%	67%
5 year	58%	54%	67%
Duration of response, years			
Median, years (95%CI)	NR (5-NR)	NR (0.4-NR)	NR (3.6-NR)
1 year	80%	68%	100%
3 year	80%	68%	100%
5 year	70%	56%	89%

NR= not reached