Subcutaneous Administration of Cytarabine for Pediatric Patients with Langerhans Cell Histiocytosis Decreases Burden of Patient Travel and Infusion Center Utilization

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Abstract

Both vinblastine and low dose cytarabine therapy for Langerhans cell histiocytosis (LCH) have historically been delivered intravenously. Due to a vinblastine shortage and the SARS-CoV2 pandemic, frontline subcutaneous cytarabine was used to treat six pediatric patients with LCH with greater than 93% of the cytarabine doses administered at home by family. On average, 164 infusion chair hours (65.7 infusions) and 5,607 miles of driving were saved per patient, highlighting that subcutaneous cytarabine is a feasible treatment option for pediatric patients with LCH resulting in notably decreased patient travel burden and infusion center utilization.

TITLE PAGE

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Abbreviations Key (for main text, not table)

Abbreviation	Full Phrase
CR	Complete response
IRB	Institutional review board
IV	Intravenous
LCH	Langerhans cell histiocytosis
PR	Partial response

Abstract:

Both vinblastine and low dose cytarabine therapy for Langerhans cell histiocytosis (LCH) have historically been delivered intravenously. Due to a vinblastine shortage and the SARS-CoV2 pandemic, frontline subcutaneous cytarabine was used to treat six pediatric patients with LCH with greater than 93% of the cytarabine doses administered at home by family. On average, 164 infusion chair hours (65.7 infusions) and 5,607 miles of driving were saved per patient, highlighting that subcutaneous cytarabine is a feasible treatment option for pediatric patients with LCH resulting in notably decreased patient travel burden and infusion center utilization.

Introduction :

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia commonly involving the skin, bones, and/or pituitary[1]. Historical standard of care treatment with intravenous (IV) vinblastine and oral prednisone has led to high 5-year overall survival rates (99% for low-risk, 87% for high-risk disease), but there are still high rates of relapsed or refractory disease (37% for low-risk, 39% for high-risk disease)[2]. Due to its effectiveness in treating relapsed/refractory LCH[3], single agent, low dose IV cytarabine is currently being compared directly to vinblastine and prednisone as frontline LCH treatment in a randomized control clinical trial[4].

The 2019 prolonged vinblastine shortage in the United States[5,6] forced consideration of cytarabine as upfront therapy for LCH. This was immediately followed by the SARS-CoV2 pandemic, which resulted in pressures to minimize in-hospital exposures and reduce infusion room utilization. With these constraints, we utilized frontline cytarabine delivered primarily subcutaneously in six pediatric LCH patients from 2019 to 2022, based on sharing decision making with patients and their families. Herein, we report the clinical responses

of the cohort, highlighting both the feasibility of in home administration of subcutaneous cytarabine and decreased patient travel burden and infusion center utilization.

Methods :

Review of pediatric LCH cases from 2019-2022 was authorized by University of Michigan IRB with informed consent waived, in accordance with local research regulations. Six patients who received frontline cytarabine monotherapy at 100 mg/m^2/dose for 5 days, every 21-28 days, to complete 14 cycles were identified. Cytarabine was administered via subcutaneous injection at home, and intravenously or subcutaneously when administered in inpatient hospital or infusion center. Oral trametinib was added to treatment regimen for patients 4 and 6, due to lack of complete response, at a dose of 0.02 mg/kg/dose (rounded to nearest 0.25 mg, max 2 mg) given once daily.

Disease evaluation imaging was performed at baseline and after 2 cycles, 4 cycles (if not yet in CR), and end of therapy.$BRAF^{V600E}$ mutation analysis was evaluated by local immunohistochemistry stain on tissue biopsy and by external CLIA-certified quantitative PCR assay on peripheral blood. Complete response (CR) was based on RECIST imaging criteria, lack of metabolic activity on PET/CT, and eradication of$BRAF^{V600E}$ cells in peripheral blood (if present at diagnosis). Partial response (PR) was defined by RECIST imaging criteria, residual metabolic disease on PET/CT, or residual, detectable peripheral blood $BRAF^{V600E}$.

Results :

Demographics . Six pediatric LCH patients were treated with upfront cytarabine monotherapy (Table 1). Patients ranged from 18 months to 15 years at time of diagnosis (average 8 years). Patients 3, 4, and 6 had multisystem LCH, patients 1 and 2 had multifocal osseous LCH, and patient 5 had localized disease, but high CNS risk given pituitary involvement. Half had the classic $BRAF^{V600E}$mutation present either on tissue biopsy or peripheral blood.

Chemotherapy dose administration location . Following one instructional session performed in clinic by a registered nurse, 93.81% of cytarabine doses were administered subcutaneously at home by patients' parents, while the remainder were administered in the infusion center or inpatient hospital (Figure 1). Home administration saved patients an average of 65.7 infusion days, translating to 164 infusion chair hours per patient. Additionally, patients saved an average of 5,607 miles (range 3,024 – 7,560 miles) of driving throughout the course of their 12-month therapy, versus if they had to travel to the infusion center each of the five days per treatment cycle.

Adverse events . All six patients tolerated cytarabine treatment well, with minimal adverse events. Blood counts were monitored weekly, and while 5 of 6 patients experienced grade II anemia, none required red blood cell or platelet transfusions. There was an average of 0.5 hospital infusion visits per patient for indications other than chemotherapy (range 0-2), all for central access or de-access. Patients had an average of 1.67 emergency department visits (range 0-4), for fever or other infectious symptoms (all grade I), and an average of 0.67 hospital admissions (range 0-2), either for initial chemotherapy (i.e. for increased monitoring for patients with central diabetes insipidus) or for neutropenic fever (only one patient experienced grade III febrile neutropenia).

Outcomes. All six patients completed 14 cycles of cytarabine, with four achieving a CR and two achieving a PR (Table 1). CR's occurred early following the second cycle in patient 1 and fourth cycle in three patients. In the two patients with a PR, one achieved a CR after addition of oral trametinib, and one had improvement on PET CT, MRI, and clinical skin exam, but continued to have positive peripheral blood$BRAF^{V600E}$ testing at end of cytarabine treatment and therefore was initiated on oral trametinib therapy.

Discussion :

While cancer drug shortages, e.g. the vinblastine shortage, directly impact patient treatment selection[6], the SARS-CoV2 pandemic influenced therapeutic decisions with a unique aspect of minimizing in-person interactions when safe and feasible. In fact, a survey of oncology providers during the SARS-CoV2 pandemic

found that 47% changed treatment selection to specifically reduce in-person visits[7]. Given that LCH-III treatment involves up to 26 infusion center visits for intravenous vinblastine[2], and the current phase 3 randomized control trial comparing vinblastine to cytarabine involves 70 infusion center visits for intravenous cytarabine[4], we similarly sought strategies to reduce in-person visits for LCH care with a transition to subcutaneous cytarabine.

Subcutaneous cytarabine is regularly used at equivalent dosing to intravenous cytarabine in pediatric patients with hematologic malignancies, at a similar low dose as used in this case series[8,9]. Its use in LCH was recently described in three pediatric patients as well[10]. Interestingly, subcutaneous cytarabine may have outcome advantages over short infusion intravenous administration with a higher area under the curve, potentially resulting in higher intracellular concentrations[11], without the requirement for central venous access.

This case series demonstrates that subcutaneous cytarabine administration was palatable to LCH patients and their families, requiring a single nurse education session to learn the proper technique for subcutaneous injections. Importantly, subcutaneous therapy was also safe, with only one grade III adverse event occurring (uncomplicated febrile neutropenia). Furthermore, patients had only 0.5 infusion visits for indications other than chemotherapy and only 1.67 emergency department visits. No blood transfusions were required in this cohort.

Over 93% of all cytarabine doses were administered at home, offering patients more flexibility and less time missing work or school. Subcutaneous cytarabine saved patients and their families an average of 5,607 miles of driving to and from medical centers throughout the yearlong course of therapy, with patients living 27-63 miles from the hospital, likely having positive downstream effects on decreasing financial pressures related to travel. Utilizing subcutaneous cytarabine saved an average of 65.7 infusion visits per patient, totaling 164 hours of infusion chair time. While this was especially important during the SARS-CoV2 pandemic, it remains valuable as pediatric infusion centers work to manage escalating patient volumes.

The clinical responses observed suggest that subcutaneously administered cytarabine is safe and feasible in pediatric LCH patients. This may have additional benefits, especially improving access to care for patients geographically distanced from pediatric LCH specialists/infusion centers, considering opting out of central lines and offering opportunities for improved quality of life while receiving LCH therapy. However, prospective trials are needed to determine the optimal frontline therapy for pediatric LCH, with at least two currently ongoing[4,12].

Conflicts of Interest:

Author K. Walkovich discloses the following potential conflicts of interest: she is the local principal investigator for the Mavorixafor trial (sponsored by X4 Pharmaceuticals); she is a member of the steering committee for Sobi; and she is on the advisory board for Sobi, Pharming, AstraZeneca, Horizon, and X4 Pharmaceuticals. None of these are relevant to this study however. The remaining authors have no relevant conflicts of interest to disclose.

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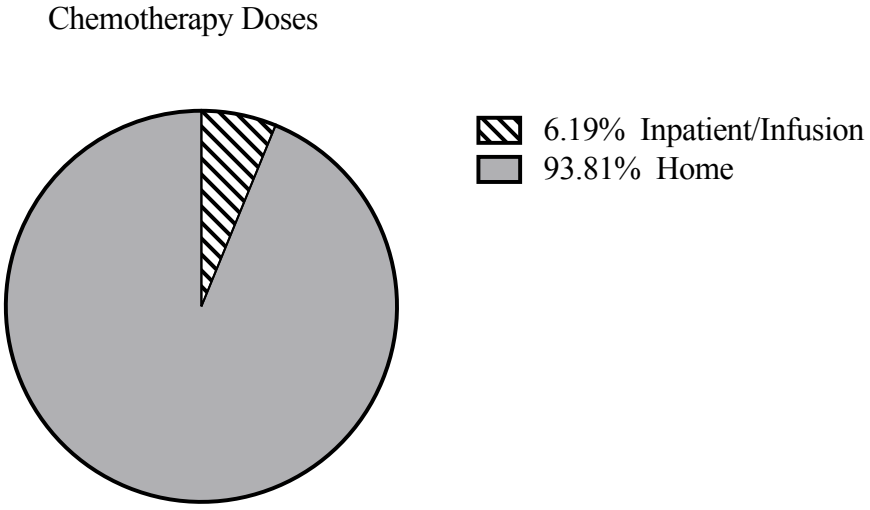
Legends:

Table 1. Patient Case Summary

Figure 1. Delivery location of chemotherapy administration. Each patient received a total of 70 doses of cytarabine (14 cycles, each 5 days), for a total of 420 doses for the 6 patients described. 394 of the 420 doses (93.81%) were administered subcutaneously at home by patients' parents, while the remaining 26 doses (6.19%) were administered either in hospital infusion center or inpatient hospital.



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Blase_LCH_Table1.docx available at https://authorea.com/users/640015/articles/655138-subcutaneous-administration-of-cytarabine-for-pediatric-patients-with-langerhans-cell-histiocytosis-decreases-burden-of-patient-travel-and-infusion-center-utilization