

Failure of salvage vemurafenib therapy for refractory multisystem Langerhans cell histiocytosis with *BRAF-V600E* mutation

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Letter to the Editor

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Abstract

Background

Langerhans cell histiocytosis (LCH) has been defined as a disorder driven by misguided myeloid differentiation, with up to 50% of cases harboring the *BRAF-V600E* mutation. Salvage treatment with LCH refractory to vinblastine and steroid regimen is intractable. Vemurafenib is safe and effective in children with refractory *BRAF-V600E*-positive LCH, but the disease always reactivates with the withdrawal of vemurafenib.

Case presentation:

Here, we report the first case of *BRAF-V600E* positive LCH resistant to vemurafenib therapy but effectively salvaged by cytarabine-based chemotherapy.

Conclusions

Our case report shows that vemurafenib monotherapy might not be effective for every *BRAF-V600E*-positive refractory LCH, and cytarabine-based chemotherapy might still be a cost-effective therapeutic alternative. **Keywords:** Langerhans cell histiocytosis, *BRAF-V600E* mutation, Vemurafenib, Chemotherapy

Full Text

A 2-year-old boy was admitted to our hospital with mass in his hard palate for more than 8 months. On admission, he presented polydipsia, polyuria, rash and marked abdominal distention. He had underlying recurrent otitis media from the age of 6 months. On physical examination he showed irregular lump in hard palate (Fig. 1A), marked hepatomegaly (8cm and 10cm below the right costal margin and the xiphoid, respectively) and splenomegaly (6cm below the left costal margin) (Fig. 1A), yellowish secretions in bilateral auditory canal and rash losing freshness in the abdomen and inguinal regions. Complete blood counts were normal. Liver function test showed slightly elevated liver enzymes (ALT 97U/L, AST 108U/L) and significantly elevated γ -glutamyl transpeptidase (1228U/L). Soft tissue masses were documented in the left nasal cavity, maxillary sinus cavity and right external auditory canal by CT scanning. In addition, CT scanning found multifocal bone destructions in the bilateral maxillary sinus, local orbital surface, bilateral hard palate, superior alveolar bone and right mastoid bone. Therefore, the diagnosis of multisystem Langerhans cell histiocytosis (LCH) with involvement of risk organs was made. Biopsy of hard palate demonstrated that the lesion cells were positively stained with CD207, CD1a and S-100. Mutation analysis revealed *BRAF-V600E* mutation.

Induction chemotherapy with prednisone and vincristine combination was instituted according to the LCH-III protocol [1]. However, therapy response was judged as active disease worse, with aggravation of

severity of hepatosplenomegaly, at end of 6-week induction therapy (Fig. 1B). Hence, salvage vemurafenib monotherapy (20mg/kg/d, bid) was given to the patient. A month later, the patient achieved active disease better without side-effects (Fig. 1C). The circulating cell-free *BRAF-V600E* load decreased from 1.79% to 0.05%. Surprisingly, a new mass occurred in the oral cavity and the liver and spleen enlarged again by oral vemurafenib for two months (Fig. 1D). Unfortunately, determination of blood concentration of vemurafenib was not available. Finally, we adopted Japan Langerhans Cell Histiocytosis Study Group-02 (JLSG-02) -protocol chemotherapy [2] to control the active disease. The mass in the mouth disappeared completely and the liver and spleen become smaller after 6 weeks of chemotherapy (Fig. 1E). Besides, both secretions in auditory canal and rash dissolved, but he still need the same dose of desmopressin to control diabetes insipidus.

LCH has been defined as a disorder driven by misguided myeloid differentiation, with up to 50% of cases harboring the *BRAF-V600E* mutation [3]. Vinblastine combined with prednisone have remarkably improved the overall survival of LCH. However, LCH refractory to the standard vinblastine and steroid regimen has a poor survival. Recently, a series of studies have indicated that vemurafenib (*BRAF-V600E* inhibitor) is safe and effective in children with refractory *BRAF-V600E*-positive LCH [4], but the optimal dose and duration of vemurafenib, monotherapy or combination chemotherapy, and long-term safety profile remain to be established. To our best understanding, this patient is the first reported case of *BRAF-V600E* positive LCH resistant to vemurafenib therapy but effectively salvaged by cytarabine-based chemotherapy. Our case report shows that vemurafenib monotherapy might not be effective for every *BRAF-V600E*-positive refractory LCH, and cytarabine-based chemotherapy might still be a cost-effective therapeutic alternative. Further studies are needed to identify the risk factors associated with resistance to vemurafenib, and to better formulate individualized therapy for refractory LCH in children.

Declarations

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Authors' contributions

XG and JG designed the study. XT and ZW collected and processed data. XT and ZW wrote the manuscript. JG and XG reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data available on request from the Dr Xia Guo.

Declarations

Ethics approval and consent to participate

The study was approved by China Ethics Committee of Registering Clinical Trials (ChiECRCT20200147) and acquired the consent to participate of the patients' father.

Consent for publication

Consent was obtained from the patients' father for publication of this report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. *Blood*. 2013;121:5006–14.
2. Morimoto A, Shioda Y, Imamura T, et al. Intensified and prolonged therapy comprising cytarabine, vincristine and prednisolone improves outcome in patients with multisystem Langerhans cell histiocytosis: results of the Japan Langerhans Cell Histiocytosis Study Group-02 Protocol Study. *Int J Hematol*. 2016;104:99–109.
3. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379:856–68.
4. Donadieu J, Larabi IA, Tardieu M, et al. Vemurafenib for Refractory Multisystem Langerhans Cell Histiocytosis in Children: An International Observational Study. *J Clin Oncol*. 2019;37:2857–65.

Figures



A



B



C



D



E

Figure 1

Fig 1. The changes of mass in the patient's oral cavity and hepatosplenomegaly in different time point. A Before therapy; B treatment with prednisone and vincristine for 6 weeks; C treatment with vemurafenib for 1 month; D treatment with vemurafenib for 2 months; E treatment with JLSG-02-protocol chemotherapy for 6 weeks