Letters

RESEARCH LETTER

Vemurafenib Use in an Infant for High-Risk Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a clonal disorder characterized by lesions containing pathological CD207+ dendritic cells. Refractory high-risk LCH is a life-threatening disease that affects mostly infants. Patients with a Disease Activity Score (DAS) higher than 6, in whom vinblastine sulfate-steroid treatment had failed, have a greater than 50% risk of death, which mostly concerns children younger than 2 years.1 Because somatic $BRAF$ V600E mutation plays an important role in LCH pathophysiology,2 BRAF inhibitors could offer a new therapeutic approach3 but, to our knowledge, have never been proposed as a treatment in infants.

Methods | Our patient was an 8-month-old girl who was diagnosed as having $BRAF$ V600E-mutated LCH with skin, bone, gut, node, and spleen involvement and hematological dysfunction (DAS, 5). After the failure of 2 vinblastine-steroid inductions followed by 1 course of cladribine, her DAS was 10. Off-label treatment with the BRAF inhibitor vemurafenib was started at an initial dose of 120 mg twice daily (33.8 mg/kg/d) for 60 days after written informed consent was obtained from the parents. The tablets were split, crushed, and suspended in water for oral administration. To assess the efficacy of treatment, the DAS was determined twice per week, and we also performed computed tomographic (CT) scans using RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 criteria.7

Results | On day 3, the patient’s general health improved with apyrexia, oral feeding, decreased skin lesions, and tumoral syndrome. On day 7, the biological inflammatory syndrome disappeared, and hypoalbuminemia and anemia showed progressive improvement (Figure 1). On day 14, all signs of disease activity had disappeared (DAS, 0), and CT scan showed partial remission (Figure 2). Skin toxicity (cutaneous eruption, WHO [World Health Organization] grade 2) occurred on day 20, and vemurafenib dose was reduced to 60 mg once daily (8.5 mg/kg/d) without adverse events. A CT scan at day 60 showed complete remission, and vemurafenib therapy was discontinued. On day 90, skin relapse was diagnosed (DAS, 1). Vemurafenib was resumed at 120 mg once daily (13.3 mg/kg/d) for 2 months and was effective (DAS, 0) without adverse effects. Five months after the second discontinuation of vemurafenib therapy, the patient remains in complete remission without any sequelae. Because we used crushed, suspended tablets, we checked whether vemurafenib was detectable within plasma using liquid chromatography coupled with mass spectrometry.4 Between 2 and 8 hours after ingestion, we detected a mean concentration at 8.9 μg/mL (range, 8.2-10.3 μg/mL) at day 3 and 11.8 μg/mL (range, 9.8-13.1 μg/mL) at day 18, thus confirming absorption of at least part of the drug.

Discussion | We report the first use of vemurafenib in an infant with LCH, to our knowledge. In the absence of pharmacological data in infants, the initial dose was empirically chosen, aiming for similarity to the body weight-related adult reference dose used in melanoma treatment. Despite the low plasma concentration, possibly explained by manipulation of the tablet or by different pharmacokinetics in children,5 a quick effi-

Figure 1. Evolution of the Disease Activity Score and Blood Test Results Following Initiation of Vemurafenib Therapy

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Table: Disease Activity Score and Blood Test Results

<table>
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<tr>
<th>Measurement</th>
<th>Baseline</th>
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Efficacy of treatment was observed. Efficacy was also observed with a once-daily administration during the second course of treatment for skin. However, a once-daily administration should lead to a higher variability of vemurafenib concentration in regard to elimination half-life time at 27.3 hours as estimated in our patient.

The present report is limited in that only 1 patient is described and the follow-up duration was 10 months. We did not observe major adverse effects such as squamous cell carcinoma or renal dysfunction, and our patient’s cutaneous eruption was managed with dose reduction. A close follow-up was maintained to detect possible long-term sequelae. Pharmaceutical data are needed to support and specify the modalities of the use of crushed tablets of vemurafenib in the absence of a specific oral solution for young children. Moreover, as an ongoing study investigates the anti-BRAF drug dabrafenib in children (clinicaltrials.gov identifier: NCT01677741), a phase 1/2 study is likely mandatory for the clinical development of vemurafenib treatment for LCH, especially in infants, who are the most vulnerable to high-risk LCH.

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Successful Treatment of Non–Small Cell Lung Cancer With Erlotinib Throughout Pregnancy

Erlotinib is the standard of care for epidermal growth factor receptor (EGFR) mutated lung adenocarcinomas in the United States. However, in pregnant patients with lung cancer, chemotherapy is recommended, irrespective of EGFR mutations, given the lack of experience and uncertainty for fetus’s safety with erlotinib.

Methods | The patient, with twin pregnancy after in vitro fertilization, was intentionally treated with erlotinib. Pharmacokinetics of erlotinib were measured in the mother’s plasma and the twins’ cord blood, which were collected at delivery. The pharmacovigilance of erlotinib during pregnancy was analyzed by accessing the Roche/Genentech global database.

Results | A patient, a nonsmoking woman in her forties who was 10-weeks pregnant with dichorionic-diamniotic twins, was diagnosed as having a stage IV exon 19 deletion adenocarcinoma after a generalized seizure. The primary tumor in the right lung was 5.1 cm, with an additional smaller lesion in another lobe, and 6 cerebral metastases. After an ethics consultation, she decided to continue the pregnancy. Her brain lesions were treated by stereotactic radiotherapy during the first trimester, with adequate precautions against uterine radiation. She started erlotinib, 150 mg daily, at the start of the second trimester under close surveillance by medical oncology and obstetrics. The only adverse effects were mild skin rash and fatigue. At 33 weeks, intrauterine growth restriction (IUGR) was diagnosed in 1 twin, leading to a cesarean delivery at 37 weeks. The treatment duration of erlotinib during pregnancy was 130 days. Erlotinib was held 72 hours prior to delivery and resumed 3 weeks postpartum after proper healing. The female twins weighed 2353 and 2438 g, which were small weights for this gestational age (87% of expected) but comparable with weights of other fetuses exposed to chemotherapy. Placental pathologic evaluation revealed no metastasis. The aspartate transaminase level (Figure) was elevated, but alanine transaminase and alkaline phosphatase levels were normal. Imaging assessments at baseline and 4 weeks postpartum demonstrated a partial response to the chemotherapy. Both lung lesions became cystic, and all brain lesions were smaller. To date, at 13 months postpartum, the patient continues to receive erlotinib and works full-time. Both twins were thriving at the 12-month developmental milestone.

Erlotinib and its active metabolite, OSI-420, were measured in the mother’s plasma at 54 ng/mL, which is about 5% of the expected plasma concentration for daily erlotinib—150 mg—at steady state.1 Drug concentrations were lower in cord blood, confirming transplacental transfer, around 25% (erlotinib) and 10% (OSI-420) of the maternal plasma concentration (Figure).

Discussion | For pregnant patients with lung cancer, the standard of care is chemotherapy during the second and third trimesters, but the prognosis is poor. In a series of 9 cases, all patients died within 1 year of delivery.2 Novel cancer treatments pose therapeutic and ethical challenges. This first pharmacological report of erlotinib in pregnancy demonstrates low-

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**Figure. Pharmacokinetics of Erlotinib and OSI-420 and Aspartate Transaminase (AST) Levels in 2 Newborns**

A,B. Levels of erlotinib and its active metabolite OSI-420, respectively, in mother’s plasma and twins’ cord blood at delivery, 72 hours after the last erlotinib administration. C. Trend of AST levels in 2 Newborns. Levels of AST were measured and trended in both newborns. Reference range, 10 to 30 U/L. To convert AST to microkatal per liter, multiply by 0.0167.

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A and B. Levels of erlotinib and its active metabolite OSI-420, respectively, in mother’s plasma and twins’ cord blood at delivery, 72 hours after the last erlotinib administration. C. Trend of AST levels in 2 Newborns. Levels of AST were measured and trended in both newborns. Reference range, 10 to 30 U/L. To convert AST to microkatal per liter, multiply by 0.0167.