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Letter to *Blood*

TO THE EDITOR:

Clinical responses and persistent *BRAF* V600E^{+} blood cells in children with LCH treated with MAPK pathway inhibition

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Langerhans cell histiocytosis (LCH) is characterized by granulomatous lesions with pathologic CD207^{+} dendritic cells.[1] More than 40% of children with high-risk LCH (involving bone marrow, liver, and/or spleen) are not cured by frontline chemotherapy, with the highest risk of morbidity and mortality in those with poor initial response.[2] Uncontrolled LCH is associated with increased morbidity,[3] including progressive LCH-associated neurodegeneration (LCH-ND).[4] Activating somatic mutations in MAPK pathway genes occur in most cases of LCH, with ~60% attributable to *BRAF* V600E[5-8]; otherwise, the mutation burden is low.[6,7] Recently, *BRAF* V600E mutations were identified in mononuclear cells from peripheral blood and in brain biopsies of patients with LCH-ND, supporting LCH-ND as a tissue-specific process driven by ERK activation.[9,10]

High-dose nucleoside analogs and hematopoietic cell transplantation are effective salvage strategies, although they are associated with high treatment-related morbidity and mortality.[11-13] Given the central role of MAPK pathway activation in pathogenesis, targeted inhibition of the MAPK pathway may be an effective therapeutic strategy for LCH.[14,15] Phase 1 to 2 trials and series of adults with LCH and the related disorder of Erdheim-Chester disease (ECD) treated with the *BRAF* V600E inhibitor vemurafenib reported universal metabolic response (objective response rate of 43% when using RECIST criteria; additional studies using metabolic response criteria by positron emission tomography demonstrated objective response rates of 100%).[16-18] Discontinuation of therapy frequently resulted in relapse, with 75% of adults with ECD progressing after discontinuation of therapy in the LOVE study.[19] Although early reports of MAPK pathway inhibition in adults with LCH and/or ECD have demonstrated promising response rates, the efficacy and safety of MAPK pathway inhibition in children with LCH remains uncertain. There are few reports in pediatric LCH, although a few cases have suggested potential for responses to MAPK inhibition.[20-22] The optimal therapy for this age group is not well established, and improved strategies are urgently needed for children with refractory/relapsed high-risk LCH and LCH-ND.

NACHO-LIBRE (North American Consortium for Histiocytosis–Registry Study of LCH and Related Disorders: Inhibition of MAPK Pathway Activation [RAS, BRAF, MEK, and ERK]) was designed to systematically evaluate the efficacy and toxicity of MAPK inhibitors in a retrospective cohort of children with LCH. Institutional review board approval was obtained from Baylor College of Medicine, and NACHO member and partner institutions contributed outcomes for children with LCH (systemic and/or LCH-ND) treated with MAPK pathway inhibitors; none of the patients were enrolled in a clinical trial for these drugs. Early data from patients 1, 4, 12, and 21 have been reported previously, with extended treatment course and toxicity information reported here.[9,23]

Medical records from 21 pediatric patients with LCH (systemic and/or LCH-ND) from 14 institutions were systematically reviewed (supplemental Table 1, available on the *Blood* Web site). All patients had experienced failure of at least 1 prior therapy and had a proven MAPK pathway somatic mutation (*BRAF* V600E, n = 20; *MAP2K1*_c293_310del, n = 1; supplemental Table 1). Response assessments were based on best response using applicable criteria for each individual, according to modified RECIST 1.1 criteria specific for LCH (supplemental Methods),[24] including positron emission tomography (metabolic) criteria, bone marrow evaluation, serial brain magnetic resonance imaging, and ataxia rating score using the Scale for Assessment and Rating of Ataxia.[25] All patients were age <21 years (median age at start of therapy, 6.9 years; range, 0.4-20.7 years), with a median disease duration of 4 years before start of MAPK inhibitor (range, 0.07-18.4 years) and median of 3 prior treatments (range, 1-9 treatments). At the start of MAPK inhibition, 13 patients had LCH-ND (clinical and radiographic evidence of disease, n = 11; radiographic evidence only, n = 2); the remaining 8 patients had systemic disease without LCH-ND (7 with high-risk organ involvement). Patients were treated for a median of 12.4 months (range, 0.6-44.6 months), with a median follow-up time of 13.3 months (range, 0.6-45.8 months) from start of MAPK inhibitor therapy. Reasons for treatment discontinuation are noted in supplemental Table 1.

Overall response rate was 86% for the entire cohort based on best response using RECIST criteria modified for LCH (supplemental Table 1; supplemental Methods). Four (19%) of 21 patients achieved a complete response (CR), and

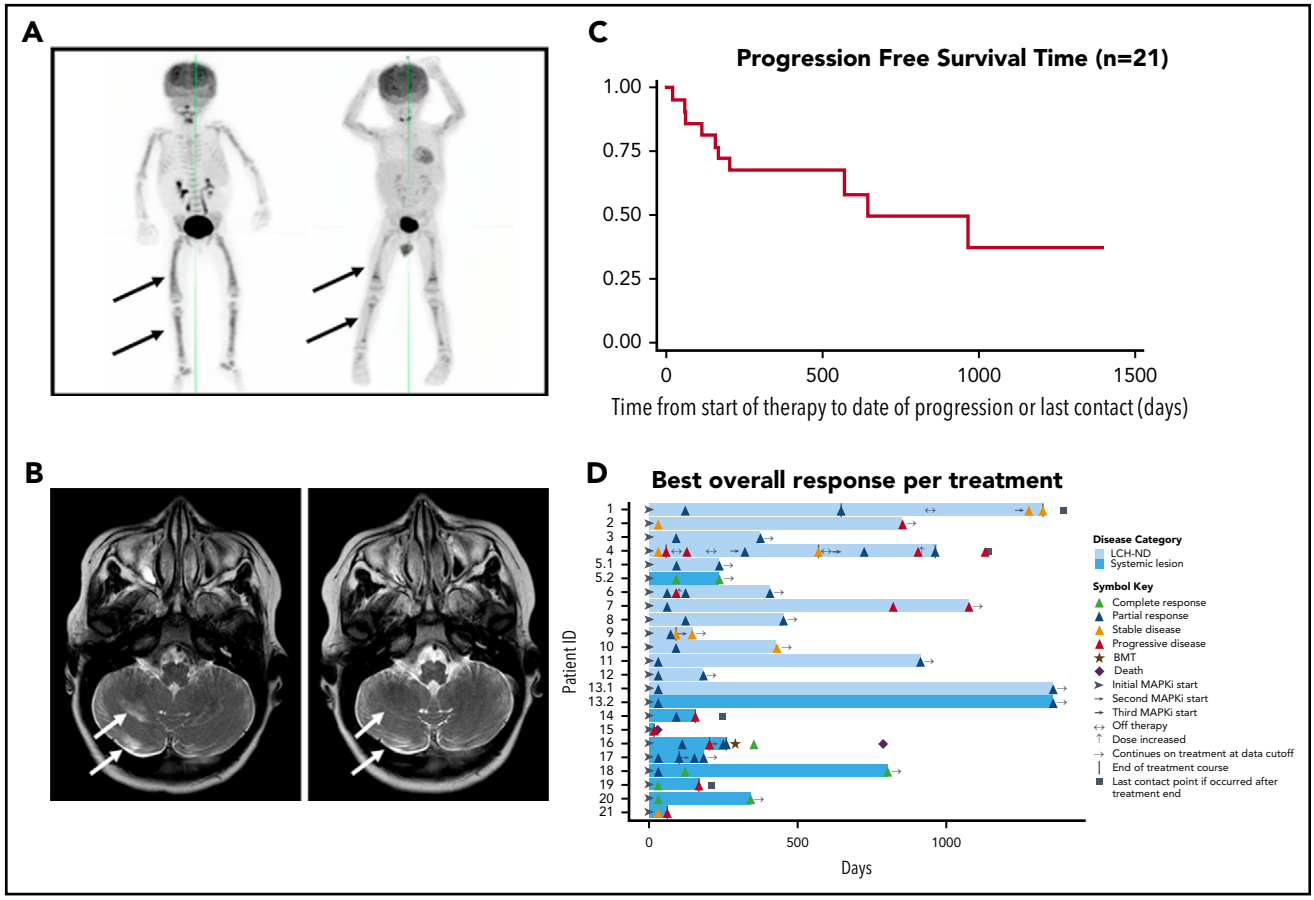

Figure 1. Outcomes of pediatric LCH patients treated with MAPK pathway inhibitors. (A) [^{18}F]fluorodeoxyglucose–positron emission tomography scan from patient 17 with disseminated high-risk LCH before (left) and 2 months after (right) treatment with vemurafenib, scored as a partial metabolic response. (B) Magnetic resonance imaging brain (axial T2 fluid-attenuated inversion recovery) from patient 6 with radiologic LCH-ND before (right) and 7 months after (left) treatment with vemurafenib, scored as a partial radiologic response. (C) Graphic representation of progression-free survival (PFS) time (37%) for all patients treated with MAPK inhibition (MAPKi; n = 21). (D) Individual swimmer plots for each patient (n = 21), depicting PFS with MAPKi. Responses for patients (5 and 13) who had both LCH-ND and systemic LCH at start of MAPKi are subdivided as follows: 5.1, swimmer plot for LCH-ND; 5.2, swimmer plot for parietal bone lesion; 13.1, swimmer plot for LCH-ND; 13.2, swimmer plot for LCH liver involvement. BMT, bone marrow transplantation.

14 patients (67%) achieved a partial response (PR), whereas 2 patients (10%) achieved stable disease (SD), and 1 patient (4%) died early during therapy as a result of progressive disease complicated by secondary macrophage activation syndrome (supplemental Table 1; Figure 1). Of the 13 patients who had any LCH-ND, none achieved a CR, but 12 (92%) achieved a PR and 1 patient (8%) maintained SD by either clinical or radiographic assessment (supplemental Table 1). Of the 10 patients who had any other LCH disease at start of therapy, 4 (40%) achieved a best response of CR, 3 (30%) achieved a PR, 1 (10%) had SD, and 1 (10%) had progressive disease.

Patients who had a shorter duration of LCH-ND or were clinically asymptomatic before start of MAPK inhibitor tended to have the best response to MAPK inhibition (supplemental Table 1). Median progression-free survival time after start of therapy was 14.2 months (range, 4.6-44.7 months). Among those who experienced an event, median time to disease progression or recurrence was 2.8 months (range, 0.6-21.2 months). Kaplan-Meier progression-free survival estimate from start of therapy to last contact was 37% (median follow-up time, 14 months; range, 0.6-46.5 months), and overall survival was 90% (1 death resulting from transplantation-related mortality; Figure 1). Four (19%) of the 21 patients experienced grade 3 or 4 toxicity, and 2 patients required dose modification. Five patients (24%) received concurrent therapies (supplemental Table 1).

Ten patients had measurable *BRAF* V600E–mutated peripheral blood mononuclear cells (PBMCs) or bone marrow cells before the start of MAPK inhibition, with subsequent molecular assessments obtained after start of MAPK inhibitor. In contrast to patients treated with chemotherapy, in whom the presence of *BRAF* V600E^{+} PBMCs reflects disease burden,[11] the percentage of *BRAF* V600E^{+} PBMCs in patients treated with MAPK inhibition in this series did not reliably correlate with disease activity or clinical response (supplemental Figure 1).

In this multisite retrospective review of patients with multiple previous treatment failures, MAPK pathway inhibition was associated with an overall response rate of 86% and no treatment-related mortality, which compares favorably to alternative chemotherapy salvage strategies.[12,13] These data are valuable as a collection of experiences from a challenging cohort of LCH patients for whom previous therapies failed. Patients with relapsed/refractory high-risk systemic LCH generally experienced early benefit from this strategy, although few achieved a sustained CR. Patients with relatively early onset of LCH-ND had better radiologic and clinical responses compared with patients with longstanding LCH-ND.

We hypothesize that inhibition of the MAPK pathway may confer clinical benefit by blocking differentiation and proliferation of precursor cells with hyperactive MAPK signaling.[15] However, MAPK inhibition may have limited cytotoxic potential, as supported by persistence of *BRAF* V600E^{+} mononuclear cells in blood and bone marrow, even in patients with impressive clinical responses, and relapse after discontinuation of therapy. If MAPK inhibition arrests pathogenic mechanisms but does not kill LCH precursor cells, alternative approaches may therefore be necessary for cure. For example, combination of MAPK inhibition with conventional cytotoxic chemotherapies may be a consideration for future trials to test potential to achieve sustained clinical improvement and eradicate the underlying precursor cells. Acknowledging intrinsic limitations of multicenter retrospective series, this study demonstrates potential for patients with refractory or relapsed LCH or LCH-ND to respond to MAPK inhibition. Future prospective trials are required to determine optimal patient population, timing and duration of MAPK inhibition, mutation-specific responses to specific inhibitors,[26] and potential for improved outcomes with strategies that combine MAPK inhibitors with other targeted agents and/or chemotherapeutic agents for children with LCH.

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Authorship

Contribution: C.E.A. and C.R.-G. conceived of the study and managed study design, oversight, and analysis; O.S.E. implemented the study, analyzed data, and drafted the manuscript; J.V. contributed patient data and reviewed the manuscript; and all authors reviewed and approved the final manuscript. Members of the NACHO-LIBRE Study Group participated in study design and analysis, and reviewed and approved the final manuscript.

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A complete list of the members of the NACHO-LIBRE Study Group appears in "Appendix."

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Footnote

The online version of this article contains a data supplement.

Appendix

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