Dabrafenib and trametinib in Langerhans cell histiocytosis and other histiocytic disorders

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Abstract

The standard treatment for Langerhans cell histiocytosis (LCH) is chemotherapy, although the failure rates are high. Since MAP-kinase activating mutations are found in most cases, BRAF- and MEK-inhibitors have been used successfully to treat patients with refractory or relapsed disease. However, data on long-term responses in children are limited and there are no data on the use of these inhibitors as first-line therapy. We treated 34 patients (26 with LCH, 2 with juvenile xanthogranuloma, 2 with Rosai-Dorfman disease, and 4 with presumed single site-central nervous system histiocytosis) with dabrafenib and/or trametinib, either as first line or after relapse or failure of chemotherapy. Sixteen patients, aged 1.3-21 years, had disease that was recurrent or refractory to chemotherapy, nine of whom had multisystem LCH with risk-organ involvement. With a median treatment duration of 4.3 years, 15 (94%) patients have sustained favorable responses. Eighteen patients, aged 0.2-45 years, received an inhibitor as first-line treatment. All of these have had sustained favorable responses, with a median treatment duration of 2.5 years. Three patients with presumed isolated central nervous system/pituitary stalk histiocytosis had stabilization or improvement of their disease. Overall, inhibitors were well tolerated. Five patients with single-system LCH discontinued therapy and remain off therapy without recurrence. In contrast, all four patients with multisystem disease who discontinued therapy had to restart treatment. Our data suggest that children suffering from histiocytoses can be treated safely and effectively with dabrafenib or trametinib. Additional studies are, however, needed to determine the long-term safety and optimal duration of therapy.

Introduction

Histiocytic diseases are rare neoplastic disorders resulting from the aberrant accumulation of cells of the monocyte lineage, namely macrophages or dendritic cells.[1] The most common and well-studied histiocytic disease is Langerhans cell histiocytosis (LCH), a condition characterized by accumulation of clonal CD1a$^+$ and CD207$^+$ cells.[2] LCH affects approximately one in 200,000 children and is most common in children 1 to 3 years old, but can present at any age.[3] Clinical manifestations of LCH are highly variable, ranging from isolated, self-limiting lesions to multi-organ disease that is associated with significant morbidity and mortality. Traditionally, the first-line treatment for LCH has been vinblastine and systemic steroids, based on the last international randomized controlled study nearly a decade ago (called LCH-III).[4] Patients with multisystem (MS) LCH with involvement of liver, spleen, or bone marrow i.e. with so-called risk-organ involvement (RO$^+$), have a variable course, with only about 60% achieving a status of not having active disease after 1 year on standard LCH-III therapy. In MS-LCH without risk organ involvement (MS RO$^-$), the relapse/reactivation rate after 1 year of standard therapy with vinblastine and prednisone is still about 37%.[4] Second-line agents have included cytarabine and/or cladribine, or clofarabine for recurrent disease or for disease that failed to respond to standard of care.[5] These chemotherapy treatments carry a high risk of morbidity, require central access for the duration of treatment, and are not always effective in MS RO$^+$ and central nervous

system (CNS) disease.[6] These regimens are associated with severe hematologic toxicities, often requiring transfusion support, as well as delayed immune reconstitution and grade IV neutropenia, with associated blood stream infections. These toxicities are a high price to pay given the persistent risk of disease reactivation both during and after therapy.[5]

The ontology of LCH lesions has been linked to bone marrow-derived myeloid dendritic precursor cells. Activating mutations in the mitogen-activated protein kinase (MAPK) pathway play a central role in the pathogenesis of LCH.[7-13] Approximately 50-60% of LCH lesions harbor a recurrent activating mutation in the *BRAF* gene, specifically *BRAF*-V600E.[14,15] Furthermore, even in cases without the *BRAF*-V600E mutation, there is ubiquitous activation of downstream phosphorylated kinases, phospho-MEK and phospho-ERK. This suggests that activation of the BRAF-MEK-ERK axis is universal in this disease, regardless of *BRAF*-V600E mutational status.[16] Given these findings, there has been growing interest in BRAF-MEK-ERK pathway inhibitors for the treatment of histiocytic diseases. Several studies have shown that BRAF and MEK inhibitors hold promise as salvage therapy for the treatment of high-risk LCH, particularly for patients with multisystem disease or those with risk organ involvement.[17-24] The utility and feasibility of these treatments as first-line therapies have yet to be elucidated.

Herein, we describe our experience using dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, to treat LCH and other histiocytic disorders. We initially treated several children whose disease was refractory to conventional treatments or who had relapsed after therapy. Based on the observed responses and safety profiles in these patients, we offered targeted, first-line inhibitor therapy to newly diagnosed patients. All patients were treated off-label as described in detail under the methods section.

Methods

Background rationale for treating patients with inhibitors

Several children were referred to us for refractory or relapsed LCH. With consistent positive results of dabrafenib and trametinib in these patients, we proposed a clinical trial of inhibitors in the first-line setting to several companies.[17,25] However, none was able to support a trial. We therefore offered newly diagnosed patients the choice of treatment with conventional chemotherapy or an inhibitor. The justifications of this approach were the demonstrable efficacy of inhibitors in patients with refractory disease, and our goals of treatment, namely restoration of health and prevention of disease recurrence. The benefits and risks of conventional and targeted therapies were discussed in detail with the patient/parent, including the unknown potential for cure and unknown duration of optimal therapy for the latter. Patients and families were informed in detail about the off-label use of the agents and all were given the option of treatment with conventional chemotherapies. Patients receiving inhibitors were monitored for adverse effects with regular complete blood counts, blood chemistry panels, and echocardiograms. The Institutional Review Board of Cincinnati Children's Hospital Medical Center certified this retrospective study as exempt from oversight and from requiring informed consent.

The diagnosis was confirmed via histopathology, when tissue samples were attainable (n=28), by expert pediatric pathologists (RL and JP). LCH was classified as single system or multisystem, and being with or without involvement of risk organs (liver, bone marrow, spleen). Mutations were identified by VE1-immunohistochemistry (*BRAF*-V600E) or next-generation sequencing. Patients with diabetes insipidus and accompanying imaging findings of isolated pituitary stalk infiltration/thickening and/or loss of a posterior pituitary bright spot were classified as having isolated pituitary lesions. Other CNS manifestations (abnormal T2 signal in cerebellar nuclei or white matter, pontine lesions, cerebellar atrophy) were classified as isolated CNS LCH or neurodegenerative LCH. In cases of isolated pituitary or CNS disease, the presumed diagnosis was based on location and radiological characteristics.

Outcome measures

Clinical status and radiological changes were used to assess response to therapy following the Histiocyte Society guidelines. Overall responses were classified as no active disease, active disease that was better since starting therapy, active disease that was progressing, or active disease that was stable. For patients with irreversible diabetes insipidus the response was recorded separately from overall disease response. For example, in patients with MS-LCH and diabetes insipidus, complete resolution of non-pituitary disease was recorded as no active disease with diabetes insipidus. Similarly, for patients with irreversible sclerosing cholangitis present at the time of initiating inhibitor treatment, the overall disease response was separated from the liver disease (e.g., no active disease with sclerosing cholangitis).

The imaging modalities used to assess response to treatment included positron emission tomography - computerized tomography scan (PET/CT), magnetic resonance imaging, CT scan, and ultrasound. For PET scans, the initial maximum standardized uptake value (SUVmax) was compared to the SUVmax of the same lesion on the first follow-up PET/CT for patients who had a PET/CT scan on record at the time of starting the inhibitor and at follow-up within 1 year of starting the medication. PET findings were considered to indicate progressive disease, stable disease, improved disease, or complete resolution

based on interval changes in SUVmax values, as well as the number of lesions. There was not an absolute SUV value that was used as a negative cutoff. When looking at the response of LCH lesions to treatment, lesions were compared to the local background. For example, we would determine whether a skeletal lesion continued to have uptake greater than the adjacent uninvolved bone or whether a liver lesion still had uptake above that of the uninvolved liver. This classification was then used in conjunction with clinical status to determine the overall response.

BRAF-V600E mutation detection by droplet digital polymerase chain reaction

When feasible, patients with a known *BRAF*-V600E mutation had their peripheral blood analyzed for the presence of circulating mutant cells by real-time polymerase chain reaction (RT-PCR) or by droplet digital polymerase chain reaction (ddPCR) (using DNA derived from peripheral blood mononuclear cells, available at our institution as HistioTrak). The platform for HistioTrak is a standard ddPCR system (BioRad, Inc) that is optimized to maximize signal-to-noise ratio at mutation levels that are below a variant allele frequency of 0.01%. Fractional abundance or a variant allele frequency <0.001% is considered a negative result. The term "significant or not significant" is not used for clinical reporting of HistioTrak results.

Results

This study was a single-center, retrospective chart review of 34 patients with histiocytic disease who were treated with dabrafenib and/or trametinib. The patients' characteristics and outcomes are tabulated in Tables 1 and 2. Thirty-four patients (12 females, 22 males) aged 0.2 to 45 years old were treated with targeted inhibitor therapy. Sixteen patients had received systemic treatment for their histiocytosis prior to initiation of the inhibitor and 18 received the inhibitor without prior treatment (see details under Methods). The median age of the patients at diagnosis was 2.3 years and the median age at the start of inhibitor therapy was 1.9 years. The patients' characteristics, average time on inhibitor treatment, risk organ involvement, mutation, site(s) of disease, inhibitor used, histiocytic disease classification, response at last follow-up, and adverse effects are detailed in Table 1 for those with relapsed/refractory disease and in Table 2 for those treated with a targeted inhibitor as first-line therapy.

Patients receiving inhibitors who were refractory to prior treatment

Details of the 16 patients who received the targeted inhibitor after undergoing earlier histiocytic disease-specific therapy can be viewed in Table 1. Thirteen patients had biopsy-confirmed LCH; nine patients had MS RO$^+$ disease and four patients had multisystem disease without involvement of risk organs (MS RO$^-$). Of these, one had MS RO$^+$ LCH with CNS involvement and one had MS RO$^-$ LCH with pituitary stalk involvement. One patient had isolated CNS involvement (central diabetes insipidus, progressive ataxia and cognitive dysfunction) that could not be biopsied because of the location of disease, however the imaging findings were highly characteristic of LCH (loss of posterior pituitary bright spot, abnormal T2 signal in white matter and cerebellum, and progressive cerebellar volume loss). Two patients had systemic Rosai-Dorfman disease (patient #15: lymph node and CNS disease; patient #16: skin, bone and lymph node disease). Of the 14 patients with tissue samples available for analysis, 13 had mutations in BRAF-MEK-ERK pathway genes (*BRAF*-V600E, n=12; *MAP2K1*, n=1). In this cohort, the median age of initiation of inhibitor treatment was 2.4 years (range, 1.3-31). Seven patients received dabrafenib, seven received trametinib, and two patients received both drugs simultaneously. The rationale for the combination therapy for patient #14 was the unknown mutation and the lack of data on the impact of inhibitors in CNS LCH at the time of initiation of treatment, while for patient #15 dabrafenib was added to help to reduce the acneiform rash with trametinib.[26] The median length of time that this group has been treated with the inhibitor is 4.3 years (range, 0.3-7.3 years). As shown in Figure 1, in this group, six patients with LCH no longer have active disease, six do not have active disease but have residual organ damage (4 with diabetes insipidus, 1 with sclerosing cholangitis, and 1 with both diabetes insipidus and sclerosing cholangitis). Of the two patients with Rosai-Dorfman disease, one has stable disease, while the other suffered progressive disease. The patient with isolated CNS disease (patient #14) had improvement of neurological symptoms and function.

Patients receiving inhibitor as first-line therapy

Eighteen patients were treated with targeted inhibitors as first-line therapy (Table 2). Thirteen patients had biopsy-confirmed LCH; seven patients had single-system disease, three patients had MS RO$^-$ disease (1 with CNS involvement), and three patients had MS RO$^+$ disease. Four patients with single-system LCH had solitary bone lesions and received treatment due to location (CNS risk) and/or rapid growth of the lesion or persistence of pain. There were two patients with isolated CNS or pituitary stalk lesion(s) that could not be biopsied due to the location of the disease, however their imaging findings were highly characteristic of LCH (abnormal T2 signal in white matter and deep cerebellar nuclei). One patient with isolated CNS disease (#32) was found to have circulating *BRAF*-V600E$^+$ cells via peripheral blood ddPCR, suggesting LCH as the likely diagnosis (Figure 2). Two patients had progressive systemic juvenile xanthogranuloma. In this cohort, four

Table 1. Trametinib and/or dabrafenib treatment for relapsed or refractory disease. Disease classifications, mutations, and response to trametinib and/or dabrafenib in patients who received prior therapy for their histiocytic disorder.

Pt #	Age in yrs/ Sex	Dx	Disease classification Site	Genetic mutation	Prior therapy	Age at ITx start in yrs	Inhibitor	ITx, yrs	Response at FU	Trial off ITx, Y/N	Time to recur. off-therapy	Adverse effects	PB *BRAF*-V600E RT-PCR	ddPCR Histio-trak
1	0.3/F	LCH	MS, RO+ BM, bone, skin	*BRAF* V600E	(i) VBL, CS (ii) EPEG, CS, CTX (iii) CAFdA	1.9	DAB	6.3	NAD	Y	3 wks	None	+	+
2	0.8/F	LCH	MS, RO+	*BRAF* V600E	(i) MTX, MP, ARA-C	1.3	DAB	5.7	NAD + DI	Y	10 mths	None	-	+
3	0.8/M	LCH	BM, bone, skin	*BRAF* V600E	(i) VBL, CS (ii) ARA-C (iii) CAFdA	1.9	DAB	7.3	NAD	Y	5 mths	None	-	+
4	0.1/M	LCH	MS, RO+	*BRAF* V600E	(i) VBL, CS (ii) CAFdA	1.3	DAB	5.0	NAD + sclerosing cholangitis	N	NA	None	-	Low +
5	0.8/M	LCH	BM, bone, skin, LN	*BRAF* V600E	(i) VBL, CS (ii) CAFdA (iii) ARA-C, CAFdA	1.4	DAB	6.3	NAD	N	NA	None	+	ND
6	0.4/M	LCH	MS, RO+	*BRAF* V600E	(i) VBL, CS (ii) CAFdA (iii) CS, vemurafenib, VBL	2.9	DAB	3.6	NAD	N	NA	None	+	+
7	1.0/M	LCH	Skin, bone, LN, liver, spleen	*BRAF* V600E	VBL, CS	1.7	TRA	4.4	NAD + DI	N	NA	None	+	+
8	1.0/M	LCH	MS, RO+	*BRAF* V600E	(i) VBL, CS (ii) ARA-C, CS	3.8	TRA	2.1	NAD + DI + cholangitis	N	NA	None	ND	+
9	0.5/M	LCH	Skin, LN, bone, spleen, liver	*BRAF* V600E	(i) VBL, CS (ii) CAFdA	1.3	DAB	4.2	NAD	N	NA	None	+	ND
10	0.7/M	LCH	MS, RO+	*BRAF* V600E	(i) VBL, CS (ii) ARA-C (iii) CAFdA	7.3	TRA	4.4	NAD + DI	N	NA	None	-	Low +
11	1.2/M	LCH	Skin, bone, liver, spleen, BM	*BRAF* V600E	(i) VBL, CS, MP	1.8	TRA	1.8	NAD	N	NA	Rash (DR)	-	ND
12	2.8/M	LCH	MS, RO+	*MAP2K1* Q56P	(i) ARA-C (ii) hydroxyurea, MTX	5.8	TRA	2.5	NAD + DI	N	NA	Loose stools	NA	NA
13	13.6/M	LCH	Skin, bone, liver, spleen, BM, LN	*BRAF* V600E	ARA-C	15.42	TRA	2.1	ADB	N	NA	None	-	-
14	17.4/M	LCH-ND	Isolated CNS	NA	(i) ARA-C cytarabine (ii) CAFdA (iii) MTX, rituximab	20.8	DAB, TRA	6.3	Improved neurological symptom, function	N	NA	None	-	Low +
15	11.8/F	RDD	MS, RO+	Unknown	CS	11.9	TRA, DAB	2.8	ADS	N	NA	Rash (TRA)	ND	ND
16	20.0/F	RDD	Skin, liver, PS	Unknown	(i) VBL, CS (ii) MTX (iii) CAFdA (iii) sirolimus, CS (iv) ARA-C	31.0	TRA	0.3	ADP	N	23 mths	Rash (DR)	NA	NA

Pt #: patient number; yrs: years; Dx: diagnosis; ITx: inhibitor treatment; FU: follow-up; recur.: recurrence; PB: peripheral blood; RT-PCR: real-time polymerase chain reaction; ddPCR: droplet digital polymerase chain reaction; LCH: Langerhans cell histiocytosis; MS: multisystem; $RO^{+/-}$: risk organ positive/negative; BM: bone marrow; VBL: vinblastine; CS: corticosteroid; EPEG: etoposide; CTX: cyclophosphamide; CAFdA: clofarabine; DAB: dabrafenib; NAD: no active disease; Y: yes; wks: weeks; LN: lymph node; MTX: methotrexate; MP: mercaptopurine; ARA-C: cytarabine; NAD + DI: no active disease with residual diabetes insipidus; mths: months; NA: not applicable; BM: bone marrow; N: no; ND: not done; CNS: central nervous system; TRA: trametinib; PS: pituitary stalk; DR: dose reduction; ADB: active disease, better; LCH-ND: neurodegenerative LCH; RDD: Rosai-Dorfman disease; ADS: active disease, stable; ADP: active disease, progressing.

Table 2. Trametinib and/or dabrafenib as first-line therapy. Disease classifications, mutations, and response to trametinib and/or dabrafenib in patients who did not receive prior therapy for their histiocytic disorder.

Pt #	Age in yrs/ Sex	Dx	Disease classification Site	Genetic mutation	Age ITx start in yrs	Inhibitor	ITx, yrs	Response at follow-up	Trial off ITx, Y/N	Time to recur. off therapy	Adverse effects	PB *BRAF*-V600E RT-PCR	ddPCR Histio-trak
17	0.6/F	LCH	MS, RO^+ Skin, spleen, liver, LN	*BRAF* V600E	1.1	DAB, TRA (PP)	5.0	NAD	Y	18 mths***	None	-	+
18	1.7/F	LCH	MS, RO^+ Bone, spleen, lungs, LN, BM	*BRAF* V600E	1.7	TRA	1.7	NAD	N	NA	None	+	+
19	0.17/M	LCH	MS, RO^+ skin, BM, liver, GI tract	*BRAF* V600E	0.2	TRA	1.8	NAD	N	NA	None	+	+
20	0.3/M	LCH	MS, RO^- skin, bone	*BRAF* V600E	0.7	DAB	4.4	NAD	N	NA	None	+	Low +
21	0.7/M	LCH	MS, RO^- skin, bone	*BRAF* V600E	0.7	TRA	2.9	NAD	N	NA	None	+	ND
22	36.0/F	LCH	MS, RO^- CNS, soft tissue, CNS	*BRAF* N486_P490 deletion	45.0	TRA	6.5	NAD, resolution of DI, improved cognition	N	NA	None	NA	+
23	3.8/F	LCH	SS, unifocal bone	*BRAF* V600E	3.9	TRA, DAB	2.1	NAD	Y	N	Hair loss with TRA	-	+
24	8.7/F	LCH	SS, unifocal bone	*BRAF* V600E	8.8	DAB	2.0	NAD	Y	N	Nausea	-	+
25	3.0/F	LCH	SS, unifocal bone	*BRAF* L485_P490>F	3.1	TRA	1.1	NAD	Y	N	None	NA	ND
26	9.3/F	LCH	SS, multifocal bone	*BRAF* V600E	9.4	TRA	0.3	NAD	Y	N	Rash, hair loss, grey hair (stopped)	-	Low +
27	13.6/M	LCH	SS, multifocal bone	*BRAF* V600E	13.7	DAB	4.0	NAD	Y	N	None	-	ND
28	12.3/M	LCH	SS, multifocal bone	*BRAF* V600E	12.4	TRA	1.8	NAD	Y	4 mths	Rash, abdominal pain (DR)	-	NA
29	12.1/M	LCH	SS, multifocal bone	Unknown	12.7	TRA	0.3	NAD	Y	N	None	-	-
30	15.8/M	LCH	PS	NA	15.9	TRA	3.2	Decrease size + DI	N	NA	Rash	-	Low +
31	10.5/F	LCH	Isolated CNS PS, cerebellar changes	NA	10.6	TRA	3.4	Stable size of PS lesion +DI	(DR)	-	-	-	ND
32	4.3/M	LCH	Isolated CNS PS, cerebellar changes	******BRAF* V600E	4.3	TRA	3.4	Decrease in size of PS lesion + DI	N	NA	None	-	NA
33	0.3/M	JXG	Skin, liver, spleen, BM	*TFG-RET* fusion	0.3	TRA	1.3	NAD	N	NA	None	NA	NA
34	6.6/M	JXG	Skin, CNS	*GAB2-BRAF* fusion	6.7	TRA	3.9	NAD + DI	N	NA	None	NA	NA

**Identified by droplet digital polymerase chain reaction (ddPCR) because no tissue was available due to isolated central nervous system involvement. ***Restarted 18 months after a trial off therapy when noted to be ddPCR-positive in peripheral blood. Pt #: patient number; yrs: years; Dx: diagnosis; ITx: inhibitor treatment; Y: yes; N: no; recur.: recurrence; PB: peripheral blood; RT-PCR: real-time polymerase chain reaction; ddPCR: droplet digital polymerase chain reaction; F: female; LCH: Langerhans cell histiocytosis; MS: multisystem; $RO^{+/-}$: risk organ positive/negative; LN: lymph node; DAB: dabrafenib; TRA: trametinib; PP: parental preference; NAD: no active disease; BM: bone marrow; NA: not applicable; GI: gastrointestinal; CNS: central nervous system; DI: diabetes insipidus; SS: single system; ND: not done; PS: pituitary stalk; DR: dose reduction; JXG: juvenile xanthogranuloma; NAD + DI: no active disease with residual diabetes insipidus.

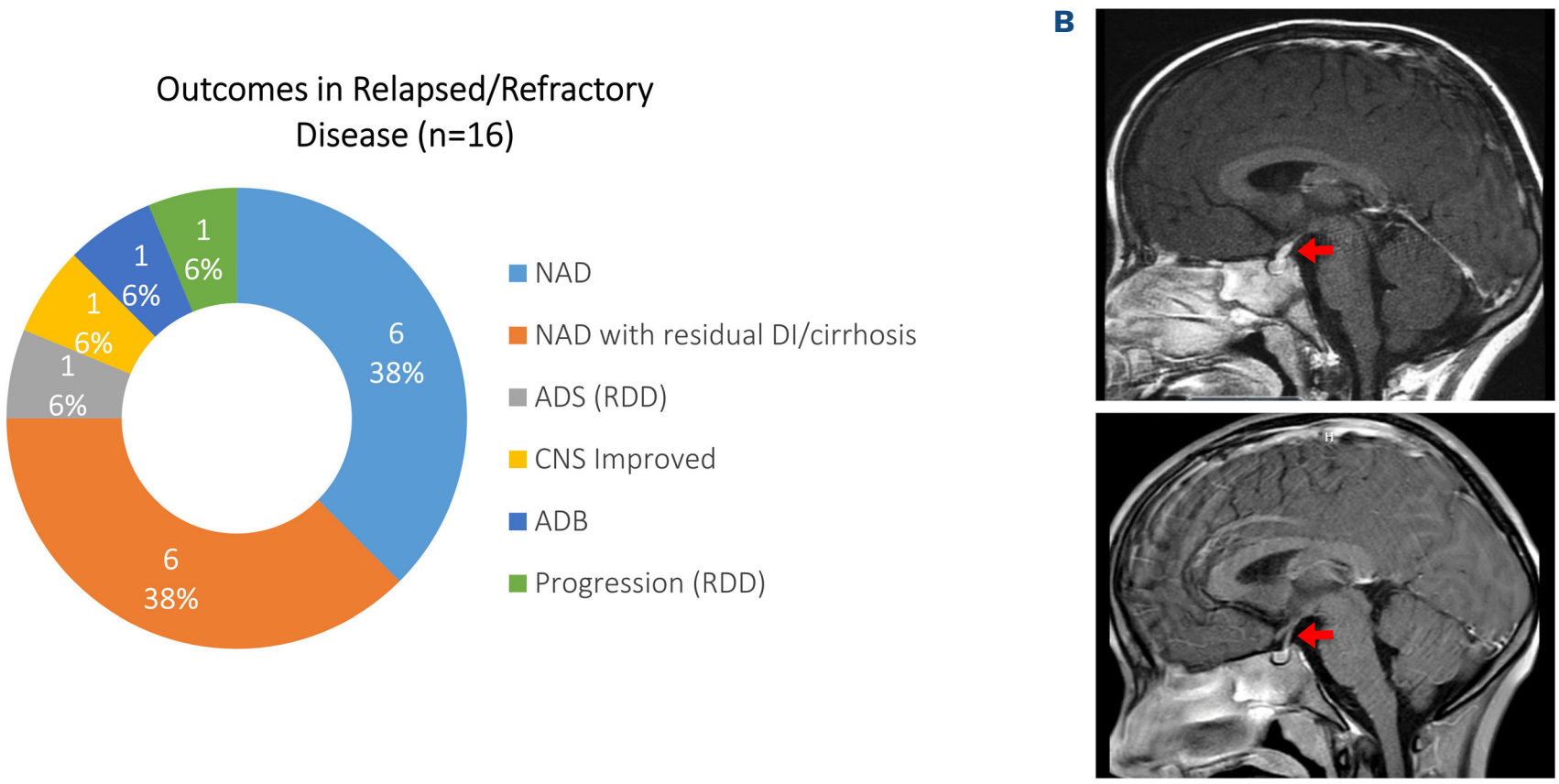

Figure 1. Response to inhibitor therapy in patients with relapsed/refractory disease. (A) Graphical summary of all responses achieved in patients with refractory/recurrent disease. Response categories are represented by the segments of the doughnut plot. (B) Post-contrast brain magnetic resonance imaging (MRI) of a 7-year-old boy with a history of recurrent Langerhans cell histiocytosis when he developed sudden onset diabetes insipidus (upper panel). The arrow points to thickened infundibulum. He was treated with trametinib and repeat MRI 6 weeks later (lower panel) showed normal thickness of the enhanced infundibulum (red arrow). NAD: no active disease; DI: diabetes insipidus; ADS: active disease, stable; RDD: Rosai Dorfman disease; CNS: central nervous system; ADB: active disease, better.

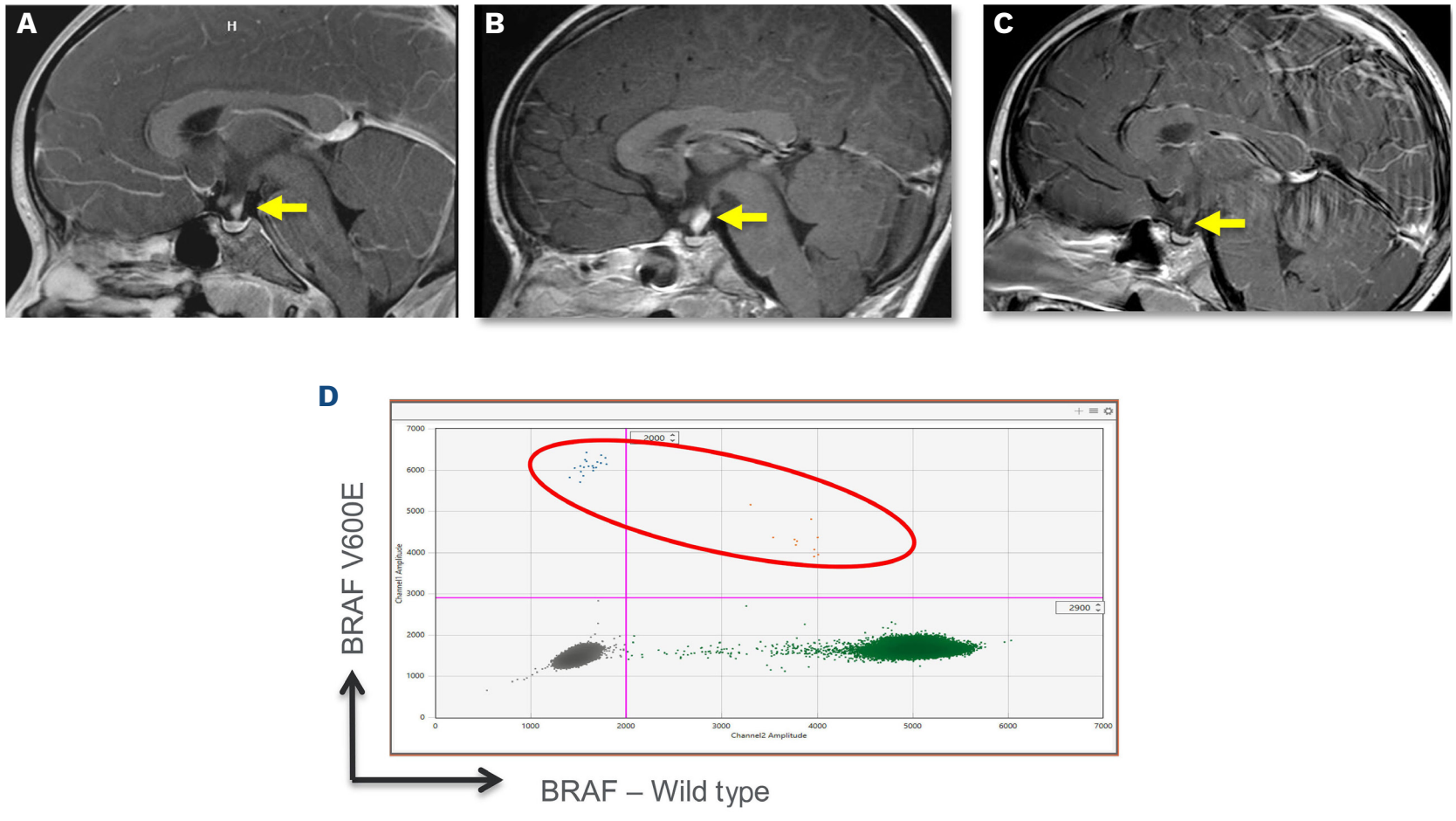

Figure 2. Isolated pituitary stalk disease diagnosed by HistioTrak. (A) Post-contrast brain magnetic resonance imaging (MRI) of a 4-year-old boy with sudden onset central diabetes insipidus, showing infundibular infiltration (arrow). Extensive evaluation was negative for histiocytosis or a germ cell tumor. A biopsy of the pituitary stalk was deemed unsafe. (B) Follow-up MRI a few months later showed worsening of pituitary stalk thickening (arrow). Treatment was initiated with trametinib. (C) Repeat MRI 3 months after initiation of trametinib showed resolution of the pituitary stalk infiltration (arrow). (D) HistioTrak on peripheral blood mononuclear DNA revealed the presence of the *BRAF*-V600E mutation (positive droplets circled).

patients received dabrafenib, 13 received trametinib, and one patient (#23) was initially treated with trametinib but then switched to dabrafenib due to side effects. Of the 13 patients with tissue samples available for analysis, 12 had mutations in BRAF-MEK-ERK pathway genes (*BRAF*-V600E, n=9; *GAB2-BRAF* fusion, n=1; *BRAF* indel, n=2). One patient with juvenile xanthogranuloma had a *TFG-RET* fusion that was identified after the patient had experienced a dramatic response to treatment with trametinib. In this group, the median age of treatment initiation was 5.5 years (range, 0.2-45) and the median treatment duration was 2.5 years (range, 0.3-6.4). As depicted in Figure 3, 12 patients with LCH currently do not have active disease, and one patient with MS RO$^-$ LCH which included CNS disease now does not have active disease, with resolution of diabetes insipidus and improved clinical neurocognition. Of the two patients with systemic juvenile xanthogranuloma (patient #33 with skin, liver, spleen, and bone marrow disease and patient #34 with CNS and skin disease), neither has active disease, although one still has diabetes insipidus. Three patients had isolated CNS or pituitary stalk disease, two of whom are currently improved, while one has stable disease.

Overall, no patients in either group experienced progression or worsening of disease on therapy, including notably patients with MS RO$^+$ disease. When available, there was a universal decrease in PET scan activity upon treatment with trametinib and/or dabrafenib (*Online Supplementary Figure S1*). Eleven patients (4 with MS RO$^+$ LCH and 7 with single-system LCH) were trialed off inhibitor therapy with four experiencing relapses of disease ranging from 3 weeks to 1 year after discontinuation with a median time of 5 months. Three of the nine relapsed/refractory MS RO$^+$ patients had a pause in treatment. All three had

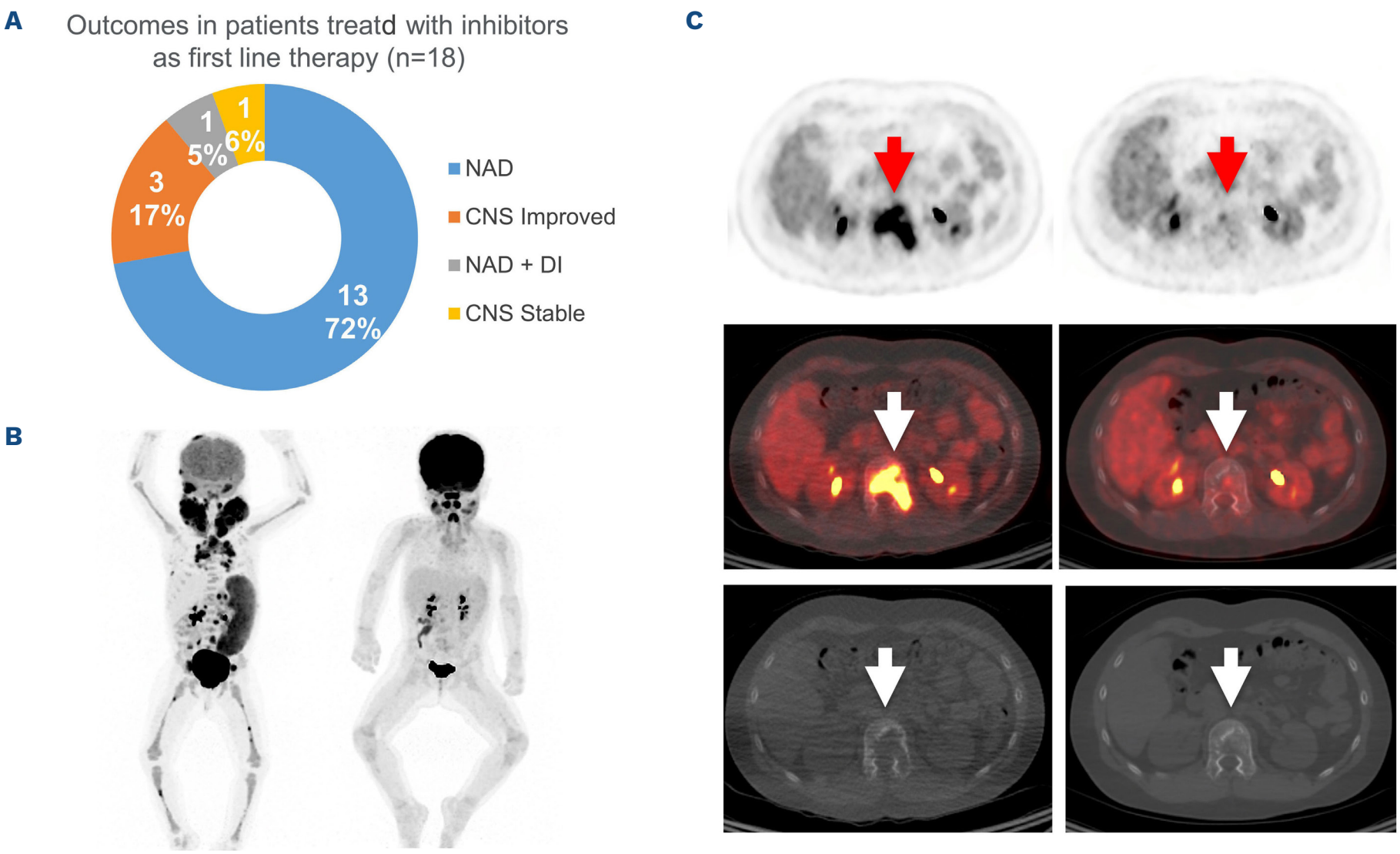

Figure 3. Response to inhibitor as first-line therapy. (A) Graphical summary of all responses achieved in patients treated with an inhibitor as first-line therapy. Response categories are represented by the segments of the doughnut plot. (B) Positron emission tomography (PET) of a 20-month-old female at diagnosis (left panel) with mixed histiocytosis with features of Langerhans cell histiocytosis and juvenile xanthogranuloma, demonstrating extensive disease including fluorodeoxyglucose (FDG)-avid lesions of the calvarium, chest wall, vertebrae, pelvis, and lower extremities, as well as splenomegaly and profound lymphadenopathy involving the neck, chest, abdomen and pelvis. Biopsy was positive for *BRAF*-V600E. Repeat imaging (right panel) following 8 weeks of therapy with trametinib, with marked interval decrease in size and FDG avidity of bony lesions, decrease in splenomegaly and marked improvement in lymphadenopathy throughout. (C) PET (upper and middle rows) and computed tomography (bottom row) of a 12-year-old male at diagnosis (left frames in each row) of multifocal bone LCH demonstrating a large bony lesion involving the L1 vertebral body, with a SUVmax value of 15. Repeat imaging (right frames) performed following 6 weeks of therapy with trametinib shows minimal FDG uptake and marked improvement of the vertebral lesion. NAD: no active disease; CNS: central nervous system; DI: diabetes insipidus.

disease recurrence, at 3 weeks, 5 months and 10 months after suspension of the inhibitor, and all achieved a status of no active disease after the inhibitor was resumed. The remaining six patients with RO$^+$ disease were not trialed off therapy and remain without active disease. One patient with single-system multifocal bone disease (no prior chemotherapy) suffered recurrence upon stopping therapy after 1 year and similarly experienced resolution of disease when the inhibitor was resumed. Only one patient receiving an inhibitor as first-line therapy with MS RO$^+$ LCH (patient #17) was taken off therapy in accordance with parental preference and with the knowledge that peripheral blood and bone marrow PCR (real time) were both negative for the *BRAF*-V600E mutation. This patient remains without active disease; however, therapy was resumed 18 months later once it was discovered that peripheral blood HistioTrak (ddPCR for *BRAF*-V600E) was positive. Six patients with single-system disease did not experience recurrence following cessation of therapy (4 patients with single-system, unifocal bone disease who were treated because the location of the lesion created a risk to the CNS or due to a rapidly growing lesion or persistent symptoms and 2 patients with single-system, multifocal bone disease). These patients were treated for a median time of 1.8 years (range, 0.3 months to 4 years) and the median time off therapy was 11 months (range, 4 months to 3.2 years).

Dosing and side effects

Patients treated with trametinib were prescribed an oral starting dose of 0.025 mg/kg daily. For young children, the 0.5 mg tablet was dissolved in 5 mL of clear liquid and the appropriate dose calculated for each patient. For patients treated with dabrafenib, the starting dosage was an oral formulation of 3-5 mg/kg daily in two divided doses. The contents of the 50 mg capsule were dissolved in 5 mL of clear liquid and the dose calculated for each child based on weight. Each dose was prepared fresh. Attributable side effects for each inhibitor are listed in Tables 1 and 2. Most of the listed side effects were considered minor. The most common reported side effect was skin rash with trametinib in six of 20 patients. The only reported side effect of dabrafenib was nausea in one of 11 patients. Four out of 20 patients on trametinib required dose adjustment due to side effects of skin rash or abdominal pain, which resolved upon dose reduction. Only one patient stopped trametinib due to side effects. Patient #23 had hair-thinning and was transitioned from trametinib to dabrafenib as per parental preference. No patients on dabrafenib needed dose adjustment.

Peripheral blood *BRAF*-V600E analysis in selected patients

For patients with *BRAF*-V600E-associated disease, peripheral blood monitoring was performed either by real-time PCR or more recently by ddPCR. The results of the most recent testing are shown in Tables 1 and 2. In most patients with MS RO$^+$ LCH, circulating *BRAF*-V600E$^+$ cells were detectable even after their disease had become inactive. Notably, in several patients we did not detect circulating *BRAF*-V600E by real-time PCR, but did see low level detection by ddPCR, highlighting the importance of using methodologies with greater sensitivity to detect the presence of residual disease cells.

Table 3. Summary of the patients' demographics, inhibitor treatment, disease classification, and mutation status.

	N (%)
Patients' demographics	
Male	22 (65)
Female	12 (35)
Total	34 (100)
Inhibitor treatment	
Dabrafenib	11 (32)
Trametinib	20 (59)
Both	3 (9)
Disease classification	
Langerhans cell histiocytosis	
Single system disease	7 (20.5)
Multisystem, RO$^-$	7 (20.5)
Multisystem, RO$^+$	12 (35)
Isolated CNS or PS	4 (12)
Total	30 (88)
Rosai Dorfman disease	2 (6)
Juvenile xanthogranuloma	2 (6)
Mutation	
Langerhans cell histiocytosis	
BRAF V600E	23 (68)
BRAF L485	1 (3)
BRAF N486	1 (3)
MAP2K1 Q56P	1 (3)
Unable to biopsy*	3 (8)
Unknown**	1 (3)
Juvenile xanthogranuloma	
GAB2-BRAF	1 (3)
TFG-RET fusion	1 (3)
Rosai Dorfman disease	
Unknown**	1 (3)
Unknown***	1 (3)

*Unable to biopsy due to location (e.g., central nervous system, pituitary stalk). **Next-generation sequencing not approved by insurance for patients #15 and #29 (VE1 negative by immunohistochemistry). ***No mutations identifiable by next-generation sequencing (patient #16). RO$^{+/-}$: risk organ positive/negative; CNS: central nervous system; PS: pituitary stalk.

Discussion

In 2017, we reported dramatic sustained clinical responses in patients with refractory MS LCH treated with inhibitors targeting the BRAF-MEK pathway.[25] Although limited by the number of pediatric patients included, several other studies have also shown sustained clinical responses to the

targeted BRAF inhibitors dabrafenib and/or vemurafenib in histiocytosis, most notably in refractory disease.[17-19] Moreover, a large pediatric international observational study recently documented that vemurafenib was effective at controlling refractory LCH with the *BRAFV*-600E mutation, albeit not curing the disease as shown by reactivation after stopping therapy.[20] A recently published prospective phase I/II study evaluated single-agent dabrafenib or the combination of dabrafenib and trametinib in pediatric patients with recurrent/refractory LCH. Clinical efficacy and manageable toxicity were seen in both treatment groups, with most responses ongoing at the end of the study.[24] Outside of pediatrics, these inhibitors have also shown efficacy in adults with histiocytic disorders.[27-29] The efficacy of targeted inhibitors as a first-line monotherapy is largely unknown, as most patients in these studies had been previously treated with conventional therapies and either did not respond or relapsed. Given the dramatic, consistent, and sustained responses seen in patients with refractory high-risk disease, we aimed to treat patients newly diagnosed with histiocytic disorders with inhibitors as first-line therapy to achieve rapid and durable disease control. Ideally, such novel treatments should be administered as part of a prospective clinical trial. Unfortunately, none of the manufacturers of the available BRAF or MEK inhibitors was able to support such a trial. With overall treatment failure rates of approximately 40% with chemotherapy compared to the almost 100% response rate with the targeted inhibitors, we chose to treat patients with the latter Food and Drug Administration-approved drugs off-label, with the goal of restoring the patient's health and preventing disease recurrence. The secondary benefits were the ease of administration while also sparing patients the potential side effects, toxicity and morbidity of traditional chemotherapeutic agents.

In our study, most of the patients had LCH and, consistent with the existing literature, the majority harbored the *BRAF*-V600E or another BRAF-MEK-ERK pathway activating mutation. All the patients with LCH or juvenile xanthogranuloma, regardless of the mutation, showed a favorable response to dabrafenib or trametinib, ranging from stabilization of disease (CNS disease, sclerosing cholangitis of liver) to complete clinical and radiographic resolution. The responses were comparable in patients treated with either dabrafenib or trametinib. Trametinib and dabrafenib each led to sustained clinical responses in patients with all classifications of disease, either as first-line therapy or in recurrent/refractory disease (Figures 1 and 3). Dabrafenib is effective only in the case of *BRAF*-V600E, while trametinib, being a MEK inhibitor, has a wider application. Once we had observed responses to trametinib in patients whose disease was driven by other mutations in *BRAF* or in *MAP2K1*, we treated all subsequent patients with trametinib, regardless of the driver mutation. One reasonable approach is to use a BRAF inhibitor in patients with *BRAF*-V600E-associated disease, and a MEK inhibitor in all the others. Our data suggest that a MEK inhibitor may be useful in all patients, regardless of the driver mutation. None of the patients in our cohorts had disease associated with RAF-independent mutations in *MAP2K1* (Class III), which are known to be resistant to allosteric MEK inhibitors such as trametinib.[30] Given their tolerability and efficacy in patients with either *BRAF* or *MAPK21* mutations, MEK inhibitors such as trametinib may be utilized initially in all patients while awaiting identification of the mutation.

It is well known that patients with MS RO$^+$ LCH are at considerable risk of disease progression despite conventional chemotherapy.[4] In concordance with previous studies, we saw sustained dramatic clinical and radiological responses, even in MS RO$^+$ patients who were refractory to chemotherapy.[18,19,21] Moreover, three patients with MS RO$^+$ LCH treated with the inhibitor as first-line therapy did not have active disease at follow-up, a status that has been sustained, making these inhibitors a potential novel therapeutic option for pediatric patients with high-risk disease. The range of disease response to therapy was largely based on classification of the disease, with the known irreversible effects such as diabetes insipidus or sclerosing cholangitis/liver cirrhosis persisting despite therapy (e.g., patients #4 and #8). The goals of treatment in these situations are to preserve organ function and prevent further progression.[31] Unfortunately, by the time these two patients were referred to us for inhibitor therapy, both had already developed extensive fibrosis in the liver, which was irreversible. In patients treated with inhibitors as first-line therapy, we hope to decrease or prevent the development of these permanent consequences. In fact, no patients in our study (in either cohort) developed diabetes insipidus, cirrhosis, or neurodegenerative LCH while on targeted therapy. Although CNS penetration of MEK inhibitors varies, these drugs remain a mainstay of brain tumor therapy for low-grade gliomas, neurofibromatosis type I and metastatic melanoma.[32] We report significant improvements for the patients in our cohort with CNS disease treated with MEK inhibition, including those with isolated CNS disease, in accordance with what was described by McClain *et al.* in their 2018 report on CNS LCH.[33] The only patient whose disease did not respond to a targeted inhibitor was patient #16, who had recurrent/refractory Rosai-Dorfman disease for 12 years that did not respond to numerous treatments and who did not have an identifiable mutation on multiple biopsies. Trametinib was tried due to persistent, severe knee pain in an area of perceived active disease. However, symptoms persisted, and trametinib was stopped when the disease progressed. The adverse effects of trametinib and dabrafenib in our study were generally mild and well tolerated with only one patient experiencing side effects significant enough to stop therapy (patient #26). It is also notable that re-

sponses were sustained at smaller doses, as seen in patients #11, #30, and #28. The discontinuation rate of the inhibitors used in our study was less than the 11.5-15.7% reported in melanoma treatment.[34] Although an increase in the risk of skin cancers has been attributed to BRAF and MEK inhibitors in the adult population, none of our patients developed skin cancer during their treatment.[35] As the average duration of treatment in our study was just over 3 years and 3 months, the longer-term tolerability remains to be elucidated.

One of the great medical challenges in treating patients with BRAF and MEK inhibitors has been the question of when to stop therapy. In our study, all patients with single-system solitary bone lesions and two of three patients with single-system multifocal bone disease experienced sustained remissions after treatment was discontinued. It is known that some patients with single-system solitary bone lesions may experience resolution of disease without treatment. As such, these lesions are not always treated and are instead monitored over time. However, in cases in which the lesion involves the cranial bones outside the calvarium, treatment is recommended due to the risk of progression to the CNS. We, therefore, cannot state with certainty whether the responses seen in this cohort were due to therapy or to spontaneous remission. The rapid resolution of symptoms and the accompanying radiographic improvement are consistent with a treatment effect. One patient with single-system multifocal bone disease (patient #28) in whom therapy was stopped at 1 year had a recurrent bone lesion shortly after discontinuation of trametinib. Resumption of treatment resulted in a rapid response that has been sustained. Additionally, all MS-LCH patients who stopped therapy experienced recurrence of disease, but regained a status of no active disease once inhibitor treatment was reinitiated. These data support others' conclusions that 1 year of inhibitor treatment is potentially insufficient outside of solitary bone lesions. Furthermore, in MS-LCH, inhibitors likely do not eradicate disease cells but rather induce clinical (silent) remission.[19,20] We detected very low levels of circulating mutant cells in the blood of many MS-LCH patients, even upon attaining complete clinical remission on inhibitor therapy. This phenomenon is thought to be due to the presence of presumed long-lived, but scantily represented, mutant bone marrow progenitor cells that serve as a reservoir of disease.[10,13,17] However, given the clinical and radiological remissions, the inhibitor therapy does effectively inhibit (render static) the mutant cell(s) from causing systemic and tissue-specific inflammatory damage to end-organs, and thus likely prevents permanent, irreversible consequences in some children (i.e., diabetes insipidus, neurodegeneration, liver cirrhosis secondary to sclerosing cholangitis) as well as quickly ameliorating the hyper-inflammatory hemophagocytic lymphohistiocytosis-like cytokine storm in MS RO$^+$ infants which carries a high risk of mortality.[36]

A highly sensitive minimal residual disease marker is needed to guide physicians on the duration of therapy based on the molecular detection of occult disease. Unfortunately, testing the blood for the circulating mutant *BRAF*-V600E cells by RT-PCR has not proven to monitor molecular remission accurately, as clinical relapses have been noted after cessation of therapy despite negative RT-PCR results.[17] In fact, when these same samples were re-tested by ddPCR on circulating mononuclear cells (not cell-free DNA), a low level of mutational burden was found. We have now developed this assay as a clinical test, called HistioTrak, to serve as a high-sensitivity biomarker for minimal residual disease. As predicted, the majority of patients with MS LCH had detectable circulating *BRAF*-V600$^+$ cells by HistioTrak, even years after inhibitor therapy. Remarkably, HistioTrak helped us to diagnose the etiology of isolated diabetes insipidus in a patient whose magnetic resonance imaging showed pituitary stalk infiltration (Figure 2). Although the diabetes insipidus persists, the pituitary stalk infiltration resolved rapidly with trametinib therapy and the child remains otherwise asymptomatic, with no clinical evidence of neurological dysfunction. However, his peripheral blood HistioTrak remains positive in spite of treatment with trametinib for 2 years. Incorporation of molecular assays such as HistioTrak will help to improve the diagnosis, treatment, and monitoring of patients with histiocytic diseases, reducing the risk of long-term complications such as neurodegenerative disease.

Despite the successful clinical remissions reached with targeted therapies in histiocytic disorders, our study is limited by being a retrospective review, not a prospective clinical trial. As such, it is difficult to deduce the efficacy of these therapies directly. We also recognize the inability of these agents to cure MS RO$^+$ LCH. Additionally, since these drugs are relatively new, the long-term safety of treatment, including its impact on fertility, is unknown. The utility of inhibitors in patients with isolated diabetes insipidus is also unknown, so treating these patients with inhibitors is not universally accepted. However, despite these limitations, our experience suggests that targeted therapies are safe and appear more efficacious in controlling disease than conventional chemotherapy, as shown by the consistent responses in both refractory and newly diagnosed disease. Prospective studies are needed in order to demonstrate efficacy rigorously. Given the rarity of this disease, it is our hope that these aggregate results will lead to prospective clinical trials that will help to answer the question of efficacy. In addition, we believe that the inability to completely eradicate mutant cells and achieve cure (defined as absence of disease without therapy) should not be the reason to discard or not utilize these life-preserving targeted therapies. There are tantalizing reports of disease eradication being attained by combining targeted therapy with chemotherapy.[37] The utility and safety of such combination approaches will need to be evaluated in larger groups of patients, probably

once a targeted therapy is approved and readily available for use in children.

In summary, patients with histiocytic disorders can be treated safely and effectively with targeted BRAF inhibitors such as dabrafenib (for those with *BRAF*-V600E mutant disease) or a MEK inhibitor such as trametinib (in disease caused by any *BRAF* mutation and most *MAP2K1* mutations). Although our data suggest that it may be possible to discontinue inhibitor therapy in single-system disease, future prospective studies are needed to determine when and if patients with multisystem disease can safely discontinue therapy. The development of highly sensitive molecular testing for minimal residual disease may help clinicians make this decision and should be incorporated into future studies. The availability of an efficacious, well-tolerated treatment for patients with high-risk disease offers a breakthrough therapeutic choice for a potentially fatal condition. Likewise, it also provides a new therapeutic possibility for patients with neurodegenerative disease for whom no effective therapy is currently available. Prospective studies are warranted to further determine the long-term efficacy and tolerability of inhibitors as first-line therapy as well as the duration of treatment.

Disclosures

AK is a consultant for SOBI, Springworks Therapeutics, and OPNA. MJ is a consultant for SOBI. AR has served on an advisory board for SOBI. The other authors have no conflicts of interest to disclose.

Contributions

EC collected and analyzed data and authored the manuscript. JF collected and analyzed data and authored the manuscript. SS and ACM reviewed radiological findings, edited the manuscript and provided the radiological figures. JP analyzed pathology specimens and edited the manuscript. RL analyzed pathology specimens. MJ, MG, AB, and AN provided clinical data. SR performed the ddPCR (HistioTrak) analysis. AK provided clinical data, supervised the entire study, and edited the manuscript.

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Data-sharing statement

Additional raw data are available upon request to the corresponding author.

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