



Annual International ECD Medical Symposium Summary

The University of Texas MD Anderson Cancer Center, Houston, TX
October 8th, 2015

The Erdheim-Chester Disease Global Alliance is pleased to provide the following summary of presentations given at this year's 3rd Annual International ECD Medical Symposium held at the University of Texas MD Anderson Cancer Center in Houston, TX on October 8th, 2015. This gathering offered a time for medical professionals to collaborate on ECD research, medical findings, and care to patients. Thank you to the presenters that presented their data and offered expertise on panel discussions, all attendees interested in learning more about ECD, and all involved in planning and making this event a success. Also, thank you to the volunteers for creating the summary for the community and the professionals unable to attend. Your time and dedication to this community are valuable and appreciated. An updated version of the summary will be published once we receive all permissions and edits.



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Keynote presentation: Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms

Eli L. Diamond, MD & Benjamin Durham, MD, MSKCC

Drs. Benjamin Durham and Eli Diamond of Memorial Sloan Kettering Cancer Center, New York, gave the keynote lecture, entitled, “Diverse and targetable kinase alterations drive histiocytic neoplasms.” Systemic histiocytic disorders, including Langerhans Cell Histiocytosis (LCH) and non-Langerhans Cell Histiocytoses (e.g., Erdheim-Chester Disease [ECD], Juvenile Xanthogranulomas [JXG], and Rosai-Dorfman Disease [RDD]) are rare diseases characterized by neoplastic histiocyte infiltration into tissues. Approximately 50% of patients with LCH and ECD have the BRAFV600E mutation, and treatment with the BRAF inhibitor, vemurafenib, confers clinical improvement in these patients. Recently, the role of the mitogen-activated protein kinase (MAPK) pathway in the manifestation of LCH was substantiated by the discovery of MAP2K1 mutations in ~25% of BRAF wild-type LCH patients. However, other than the BRAFV600E mutation, activating kinase mutations in non-LCH histiocytoses are largely undefined.

Dr. Durham presented data on an in-depth study that was undertaken in BRAF wild-type patients to determine genomic mutations and identify potential therapeutic targets. Whole exome sequencing (WES) was performed on frozen tumor biopsies from 24 adult and pediatric histiocytosis cases, 10 with LCH and 14 with non-LCH, paired with normal peripheral blood mononuclear cells. Thirteen of these patients also underwent RNA sequencing. Alterations causing activation of kinases were identified in 100% of the patients studied. Results included confirmation of the BRAFV600E and MAP2K1 mutations in LCH and the BRAFV600E and NRAS mutations in non-LCH. However, this was the first identification of MAP2K1 and ARAF mutations in non-LCH, along with 5 novel kinase fusions: RNF11-BRAF, CLIP2-BRAF, KIF5B-ALK x 2, and LMNA-NTRK1. These fusions lead to inappropriate regulation, expression and/or activation of the BRAF, ALK, and NTRK1 genes. Validation testing for kinase mutations in BRAFV600E wild type non-LCH histiocytoses revealed recurrent activating mutations in MAP2K1 (32%), NRAS (16%), KRAS (11%), PIK3CA (8%), and ARAF (3%). In addition, these gene expression analyses suggested that LCH histiocytes are derived from late-stage myeloid progenitors and dendritic cells, whereas non-LCH cells have similarity to earlier hematopoietic stem and progenitor cells and monocytes. Thus, these data show that diverse kinase mutations and fusions are a driving force in systemic histiocytic neoplasms. Furthermore, these mutations and fusions may be targets for therapeutic interventions.

Dr. Diamond continued the keynote address with data on some such clinical intervention studies. One BRAFV600E wild type patient from the above study was found to have a mutation in MEK1 (K57N). He was treated with Tremetinib, a MEK inhibitor, and showed clinical improvement. A second patient had a mutation in ARAF (S214A). Upon treatment with the kinase inhibitor, Sorafenib, there was resolution of bone pain, fevers and night sweats and

ocular steroids could be stopped. A suggested protocol for BRAFV600E wild type patients or those with the BRAFV600E mutation, but who are intolerant to BRAF inhibitors, is to genetically screen a fresh biopsy specimen and then treat with a MEK inhibitor such as Cobimetinib.

Tocilizumab for ECD

Lorenzo Dagna, MD, Vita-Salute San Raffaele University

Dr. Lorenzo Dagna of the Unit of Medicine and Clinical Immunology and Lymphoid Malignancies Laboratory, Vita-Salute San Raffaele University, Milano, Italy presented the results of a trial to evaluate the efficacy and safety of Tocilizumab in adult patients with advanced ECD not limited to the skeleton. Summary will be published soon.

Infliximab in ECD

Julien Haroche, MD, PhD, Hospitalier Pitié-Salpêtrière

Dr. Julien Haroche of the Hopital Pitie-Salpetriere, Paris, France present results on the efficacy and tolerance of Infliximab in ECD. Summary will be published soon.

BRAF inhibitors in ECD and overlap histiocytoses, an update 2015

Julien Haroche, MD, PhD, Hospitalier Pitié-Salpêtrière

Dr. Haroche also presented an update on BRAF inhibitors in ECD and other histiocytoses. Summary will be published soon.

Targeted Delivery of Hemoglobin-Cladribine Conjugate Inhibits Proliferation of Cells Originating from Human Histiocytic Lymphomas

Irina Eberle-Ayres, TheraPure Biopharma, Inc.

Dr. Irina Ayres of Therapure Biopharma, Mississauga, ON, Canada, presented work on targeted delivery of hemoglobin-Cladribine conjugate in human histiocytic lymphomas. Summary will be published soon.

Analysis of the neuro-radiological phenotypes, objective CNS responses to treatment & the long-term neuro-radiological evolution of ECD

Roei Mazor, MD, Sheba Medical Center

Roei Mazor, MD from the Chaim Sheba Medical Center, described a neuro-radiological study dedicated to analyzing the long term CNS involvement of the ECD.

This retrospective analysis included 56 MR studies on 7 out of the 12 ECD patients at Sheba, with follow up spanning over a period of 10 years.

The most frequent CNS manifestations observed in all 7 patients were involvements of the ponto-cerebellar region and absence of the neurohypophysial high intensity T1 signal before administration of gadolinium. Additional observations included the demonstration of meningiomas and involvement of the mucosa of the different sinuses. These two involvements appeared to be mutually exclusive in the Sheba cohort. Less frequent manifestations noted were retro-orbital lesions and perineural sheathing of the optic nerves, seen in one patient.

Chronologically, CNS ECD development may be divided into three consecutive, yet overlapping stages which are neurohypophysial failure, pontocerebellar lesion developments and atrophy of various brain structure. Treatment wise, chronologically appropriate responses appear in some, but not all of the ponto-cerebellar lesions pursuant treatment with interferon alpha, cladribine or vemurafenib. Additionally, the decrease in the enhancement of the sheathing of cranial nerves may serve as a marker of chronologically appropriate response.

Decreased response to treatment is evident in patients with progressive brain atrophy. As such, disease related atrophy of brain structures may indicate low neurological reserves and may confer a less favorable response to treatment and a worse prognosis. "

Does the absence of classic histology exclude ECD?

Thomas Colby, MD, Mayo Clinic, Arizona

Thomas Colby, MD is a pathologist at Mayo Clinic in Arizona. He said that ECD has been a difficult diagnosis for physicians because it's rare, there is diverse symptomatology and presentation, no one subspecialty "owns" it, no two cases are exactly the same and there is the diverse pathology of ECD.

He presented a case where there were bone lesions, skin involvement, cardio-vascular and pulmonary symptoms, retroperitoneal involvement and CNS findings. There were no classic foamy histiocytes or Touton giant cells, but the pathology was ultimately called most consistent with ECD. ECD histiologic findings include: foamy histiocytes, Touton giant cells, non-foamy histiocytes, fibrosis, lymphocytes and plasma cells; not all are present in all cases. Clues for the pathologist include: a fibrosing process that seems out of proportion to putative stimuli and may not look like "usual inflammation",

histiocytic infiltrate, foamy or otherwise, peculiar histiocytes and Touton giant cells, and a clinical suspicion of ECD or a multisystem clinical enigma.

He said the classic histology of ECD is not always present especially outside the bones. The lack of classic pathology of ECD does not exclude that diagnosis. None of the pathologic changes are unique to ECD. There are subtle histologic clues that can suggest the diagnosis. ECD needs an "owner" in one of the medical specialties.

Low –frequency KRAS mutations in patients with BRAF-mutated ECD

Filip Janku, MD PhD, MD Anderson Cancer Center

Filip Janku, MD PhD from MD Anderson Cancer Center, presented Low Frequency KRAS Mutations in Patients with Erdheim-Chester Disease and BRAF V600E mutation. Patients with ECD often have molecular aberrations in the MAPK pathway (e.g. BRAF, KRAS, ARAF, MEK). BRAF V600E mutation is the most prevalent molecular alteration, which can be effectively targeted with BRAF inhibitors. In cancers with BRAF V600E mutation emergence of simultaneous alterations in the MAPK pathway such as KRAS, NRAS, or MEK often drives resistance to BRAF inhibitors. He hypothesized that using sensitive techniques such as droplet digital PCR we can identify simultaneous low frequency KRAS mutations in the tissue from ECD patients with known BRAF mutation. Low frequency KRAS mutations can plausibly drive resistance to BRAF inhibitors.

He concluded that sensitive techniques such as ddPCR can detect previously undetected simultaneous low frequency (<1%) KRAS mutations in the tissue of patients with ECD and dominant BRAF V600E mutation. It needs to be investigated whether simultaneous low frequency (<1%) KRAS mutations can drive resistance to BRAF inhibitors. .

CLIA laboratory testing of urinary BRAF V600E DNA mutations: application in the mgmt. of patients with histiocytic disease

Adrianna Muniz, PhD & Mark Erlander, PhD, Trovagene, Inc.

Adrianna Muniz, PhD and Mark Erlander, PhD from Trovagene Inc. spoke about CLIA laboratory testing of urinary BRAF V600E DNA mutations: the application in the management of patients with histiocytic disease and urine based cfDNA. Summary will be published soon.

Accepting Illness When Loss of Function is Permanent: A Model of Functional Adaptation

Susan Robertson, PhD, NIH

Susan Robertson, PhD is an occupational therapist in the Rehabilitation Medicine Department at the NIH Clinical Center. In collaborative research with NHGRI, patients with ECD and their caregivers described their experiences before and after being diagnosed. At first, uncertainty was overwhelming, depressing, and frustrating. Once ECD was diagnosed, patients felt less healthy, but many learned to live fulfilling lives even with a chronic health condition. This involved renewing one's purpose in life, exploring ways to adjust with equipment (a cane or an adapted spoon for example), accepting the inability to control the illness, and searching for different ways to live meaningfully. "Accepting Illness When Loss of Function is Permanent: A Model of Functional Adaptation" suggested that appreciating gains from an illness may support the process of adaptation.

Oral manifestation of ECD

Juvanee Estrada-Veras, MD, [Pamela Gardner, DMD], NIH

Dr. Juvanee I. Estrada-Veras MD from the NIH, spoke about the Oral Manifestations of Erdheim - Chester Disease. Information shared during this presentation is to be published at a later date.

Cardiac health in ECD

Juvanee Estrada-Veras, MD, [William Gahl, MD, PhD], NIH

Dr. Juvanee I. Estrada-Veras of the NIH also spoke about cardiac health in ECD. Information shared during this presentation is to be published at a later date.

Diffuse reduction of cerebral grey matter volumes in ECD

Eli L. Diamond, MD, MSKCC

Eli L. Diamond, MD of MSKCC presented his study of Diffuse Loss of Cerebral Grey Matter Structures in Erdheim-Chester Disease. He found there is a loss of grey matter in ECD. Several patients have non-infiltrative disease with imbalance or frank ataxia, oculomotor abnormalities, dysphagia and in a couple cases reminiscent of neurodegenerative LCH. Cognitive difficulties have been observed without overt CNS disease. A minority of patients are working and functioning normally. Caregivers describe disinhibition, mood dysregulation, inattention and poor memory. Dr. Diamond did a study identifying structural CNS abnormalities in non-CNS ECD. A structural MRI study of 11 patients with ECD was looked at. Exploratory whole-brain comparisons of cortical thickness, subcortical volumes were compared to age-matched subjects. There was preliminary evidence of diffuse cerebral volume loss unrelated to visible ECD infiltration or treatment. A "normal MRI" is misleading and disrupts the notion of "non-CNS" ECD, which is to say that ECD probably affects the brain in many ways that we

not understand but that can impact patient's function and well-being. Further research can look at the mechanism, neurotoxicity of chronic systemic inflammation and a prospective, multimodal longitudinal study is needed.

Panel discussion: Clinical Trials in ECD

Moderator: Eli Diamond, MD, MSKCC

During this open discussion It was decided that any patient with active disease should be able to participate in trials. They want to let every patient know about clinical trials. It was brought up that maybe all centers could do the same trial. A study needs to be done to find out what areas patients are not being diagnosed.

Panel discussion: Establishing Patients' Registries and Retrospective Multi-center Outcome Analyses

Moderator: Achille Aouba, MD, Caen, France

They spoke about possibly having 1 main center and everyone sends the info to that center. The registry will make it easier for studies. MSKCC is starting a registry. It was discussed how records and specimens can be sent. It will be difficult to send specimens from other countries.