4th Annual International ECD Medical Symposium

Summary of Presentations

September 15, 2016

The Erdheim-Chester Disease Global Alliance is pleased to provide the following summary of presentations given at this year's 4th Annual International ECD Medical Symposium held on September 15, 2016 at Hôpital Pitié-Salpêtrière in Paris, France. The meeting allowed medical professionals to collaborate on ECD research, medical findings, and care to patients. Thank you to this year's co-host Professor Julien Haroche, MD, PhD, 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. Thank you to the volunteers for creating the summary for the community and the professionals unable to attend.

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Insights into the Cell-of-Origin of the Histiocytosis Using Patient-Derived Xenograft Murine Models

Dr. Benjamin Durham, Memorial Sloan-Kettering Cancer Center, USA

In 2015, they found that Langerhans cell histiocytosis (LCH) and non-LCH neoplastic cells have distinct transcriptional profiles. The BRAFV600E mutation has not been detected in the CD34+ compartment of all LCH patients. The study identifies that the CD34+ compartment in Erdheim-Chester Disease (ECD) has functional self-renewal potential and can initiate histiocytosis. The study demonstrates the first successful patient-derived xenograft of a human histiocytic neoplasm.

The Hematopoietic Origin of Adult Histiocytosis

Dr. Matthew Collin, Newcastle upon Tyne Hospital, UK

One of the aims of the study was to map the cellular origin of histiocytosis. The results showed that BRAFV600E localized to the hematopoietic stem cell in multi-system LCH, ECD and HCL and was enriched in myeloid progenitors in multi-system LCH and ECD. In peripheral blood, the pattern of BRAF mutant alleles was indistinguishable between LCH and ECD, involving predominantly monocytes and myeloid DC's.

Tailoring Treatment for Erdheim-Chester disease: focus on ECD microenvironment

Dr. Marina Ferrarini, San Raffaele Scientific Institute, Milan, Italy

The study's aim was to determine the pathogenic role of the inflammatory microenvironment expressed in ECD lesions. It was found that the ECD microenvironment is endowed with pathogenic activities that can be potentially targeted by therapeutic interventions. The RCCSTM bioreactor system is a well-suited tool for preclinical drug testing in ECD and allows one to both compare the efficacy of available drugs (including cytokine- and BRAF-inhibitors) and to explore their in situ mechanisms of action/resistance, possible leading to the identification of combination strategies for the disease.

The PD1:PDL1 Immune Checkpoint: A Possible Therapeutic Target For Histiocytic Neoplasms?

Roei D. Mazor, M.D, Sheba Medical Center, Israel

The objective of this study was to determine whether PDL1 expression occurs on the membranes of ECD histiocytes derived from multiple disease locations in multiple patients. Such expression would solidify the rationale to investigate the feasibility of immune checkpoint blockade as a therapeutic alternative in ECD. At the date of the presentation, the study encompassed 13 FFPE specimens retrieved between 2005 and 2016 from eight ECD patients with confirmed pathological diagnosis in Israel. These included specimens originating from the bone marrow (8), skin (3) and cerebellum (2). Positive controls were established using crypt epithelium and germinal center macrophages from human tonsils as previously described in the literature. Analysis of the samples demonstrated lack of staining for PDL1 in all samples and parallel positive staining for all positive controls. As such, PDL1 may not be as extensively expressed on ECD histiocytes as previously reported. Larger cohorts are necessary to determine the magnitude of PD1:PDL1 interactions in ECD.

Clinical Molecular Profiling to Detect Targetable Alterations in Archival Tumor Tissue and Cell-free DNA from Patients with Erdheim-Chester Disease

Prof. Filip Janku, The University of Texas MD Anderson Cancer Center, USA

The study found that clinical blood-based molecular testing in patients with ECD identifies targetable molecular alterations in the majority of patients. Liquid biopsy approaches appear to have higher success rates, short turnaround time and excellent concordance with results of conventional tumor tissue testing as long as they are used prior to initiation of systemic therapy.

Elevated CSF Osteopontin and Circulating Cells with BRAF Mutations in Patients with Langerhans Cell Histiocytosis-Associated Neurodegeneration -A Model for ECD?

Dr. Kenneth McClain, Texas Children's Cancer Center, USA

LCH is characterized by inflammatory lesions with pathologic CD207+ dendritic cells. Brain involvement may include mass lesions or a progressive neurodegenerative syndrome. CSF biomarkers including inflammatory proteins and extracellular BRAFV600E were evaluated in 40 patients with LCH brain lesions and/or LCH-ND. The results support a model of LCH lesions

and LCH-ND arising from a common hematopoietic precursor. The model of pathogenesis supports change in current practice to evaluate serial CSF and blood biomarkers prospectively along with long-term clinical surveillance to identify patients at risk for LCH-ND who may benefit from early initiation of therapy against the clonal reservoir of myeloid precursors with activated ERK.

Efficacy of Cladribine (2-CdA) in the Treatment of Erdheim-Chester Disease (ECD)

Dr. Ronald Go from Rochester Mayo Clinic, USA

The objective was to retrospectively assess the efficacy of cladribine in ECD. It was found that cladribine has moderate clinical activity in ECD and it is generally well tolerated and may result in durable responses.

Superior Efficacy and Equivalent Safety of Double-dose Anakinra in Erdheim-Chester Disease

Prof. Achille Aouba from Universite de Caen-Normandie, France

Anakinra has been shown to be safe and efficient in ECD. The daily single dose (SD) of 100 mg is empirical in this setting and it has been hypothesized that doubling the dose of this immunotherapy in cases of partial response or failure could improve outcomes. They found that doubling the dose to 200 mg/d was well tolerated, as well as the SD and improved global outcomes in ¾ patients including two long-term CRs. Doubling the dose of anakinra and/or its association with targeted therapies should be assessed in treatment-refractory ECD

Encouraging activity of MEK inhibitor trametinib in patients with Erdheim-Chester disease irrespective of BRAF mutation status

Prof. Filip Janku, The University of Texas MD Anderson Cancer Center, USA

A total of four patients were started on 1mg Trametinib daily. These four patients all reported some degree of improvement of their symptoms such as fatigue, pain, weakness, speech difficulties, problems with balance, fever and dyspnea. The only significant drug related toxicity was grade 2 erythematous rash. It was concluded that MEK inhibitor Trametinib at 50% of the FDA approved dose demonstrated encouraging activity in patients with ECD irrespective of underlying molecular profile.

Phase 2 Trial of Single-Agent Cobimetinib for Adults with Histiocytic Disorders: Preliminary Results

Dr. Omar Abdel-Wahab, on behalf of Dr. Eli Diamond, Memorial Sloan-Kettering Cancer Center, USA

The identification of recurrent BRAFV600E mutations in ECD led to a breakthrough in treatment of refractory or severe forms of disease with BRAF inhibition. The identification that nearly all BRAF-wildtype ECD lesions harbor mitogen activated protein kinase pathway alterations, has raised the possibility of treatment of BRAF-wildtype ECD with MEK inhibition. Of the seven patients, all evaluable target lesions have had a metabolic response, 20% a complete metabolic response, and 80% a partial metabolic response. Preliminary results from this trial demonstrate robust efficacy of single-agent Cobimetinib in BRAF wildtype ECD, RDD, and LCH. Toxicities have been manageable and similar to those observed in previous trials of Cobinetinib.

Adult Onset (Infratentorial) Leukoencephalopathy as Presenting Manifestation of Erdheim-Chester Disease

Dr. Giulio Cavalli, IRCCS H San Raffaelle Scientific Institute and Vita-Salute San Raffaele University, Italy

The etiology of adult-onset leukoencephalopathies remains unknown in about 30 to 50% of cases. Brain involvement causing infratentorial leukoencephalopathy (ITL, chiefly affecting the cerebellum and brainstem) may predate the onset of systemic manifestations of ECD. ECD emerges as a possible cause of adult-onset ITL, a finding with relevant diagnostic and therapeutic implications. Investigations aimed at unveiling ECD are indicated in all patients with ITL, even in the absence of typical clinical ECD manifestations. Diagnosing ECD may enable therapeutic strategies in patients with ITL, an otherwise untreatable, chronically degenerative condition.

MRI evidence of cardiac involvement in Erdheim-Chester disease

Dr. Augusto Vaglio, Parma University Hospital, Italy

Cardiovascular manifestations are common in ECD and include infiltration of the myocardium, the pericardium, and the aorta. ECD patients with cardiovascular involvement are reported to have a poorer prognosis and are therefore treated aggressively. Twenty-three patients were studied. Forty-three percent had MRI evidence of cardiac involvement, with myocardial

involvement in nine and pericardial in nine. Six patients had thoracic large vessel involvement together with cardiac lesions, while only one patient had thoracic aorta involvement without cardiac disease. Thoracic large artery involvement was characterized by perivascular thickening of the thoracic aorta and the origin of epiaortic arteries. Patients with cardiovascular involvement had a significantly higher number of involved organs than patients without cardiovascular involvement. MRI-detected cardiac disease does not seem to impact on survival, although this finding was limited by the low mortality rate observed. In conclusion, approximately 40% of ECD patients have cardiovascular involvement detectable by cardiac MRI; they usually have a greater disease burden than those without cardiovascular lesions. Whether they have a poorer prognosis remains to be defined

Endocrine manifestations in Erdheim-Chester disease

Dr. Carine Courtillot, Pitie-Salpetriere Hospital, Paris, France

In 64 patients, diabetes insipidus was found in 33% of patients, anterior pituitary dysfunction was found in 91.3% of patients with full anterior pituitary evaluation, including somatotropic deficiency (78.6%), hyperprolactinemia (44.1%), gonadotropic deficiency (22.2%), thyreotropic deficiency (9.5%) and corticotropic deficiency (3.1%). 35 patients (54.7%) had >_ 2 anterior pituitary dysfunctional axes, rising to 69.6% when only considering patients with complete evaluation. Two patients had panhypopituitarism. Infiltration of the pituitary and stalk was found on MRI in 24.4% cases. Testicular insufficiency was found in 53.1% patients with sonographic testicular infiltration in 29% of men. TDM adrenal infiltration was found in 39.1% of patients and one case of adrenal insufficiency was observed. No patient was free of hormonal or morphological involvement. Endocrine involvement is very frequent in ECD and should be carefully evaluated at diagnosis and during follow-up.

Panel Discussion: ECD Patient Registry: Community Tool for Retrospective Multi-Center Outcome Analyses

Moderator: Mark Heaney, MD, Columbia University Hospital

A panel discussion took place to discuss the ECD Patient Registry: Community Tool for Retrospective Multi-Center Outcome Analysis. The aims of this registry are to define the incidence of ECD, create a living and growing database, collect data meaningful to ECD by engagement with ECD patients, and to create a resource for the ECD medical community. It will

be initiated at Memorial Sloan-Kettering Cancer Center where they will collect data and patient reported data. They will have an imaging archive and pathology bank. The ECD Referral Care Centers will be the first to enrol their patients in the registry.

Panel Discussion: Proposed ECD GWAS Study

Moderator: Augusto Vaglio, MD, PhD, Parma University Hospital

A panel discussion was held to discuss a proposed ECD Genome-Wide Association Study (GWAS). There was general discussion about what would be needed to make this work, the number of samples that would be required, the benefits of the study, and the logistic implications. There was a concurrence that further investigation was needed before this study could become a reality.