Erdheim-Chester Disease

MEDICAL SYMPOSIUM

TUESDAY, NOVEMBER 16, 2021

8th ANNUAL INTERNATIONAL ECD MEDICAL SYMPOSIUM

Medical professionals from around the world gather at this annual event to share scientific findings, patient outcomes, case studies, and new developments in the research and treatment of ECD and other histiocytic disorders. The opportunity offers collaboration among scientists and encourages the expansion of a stronger physician network.

Thank you to the ECD Global Alliance Medical Advisory Board, moderators, panelists, presenters, and participants for your dedication, time, and interest!

ECD GLOBAL ALLIANCE
Supporting those affected by
Erdheim-Chester Disease worldwide.

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November 16, 2021

8th Annual International ECD Medical Symposium

Virtual Conference

Dear Participants,

Welcome to the 8th Annual International ECD Medical Symposium! Thank you for your attendance and participation. The ECD Global Alliance has worked with their Medical Advisory Board to make this year's event possible.

The ECD Medical Symposium is typically held annually in person at a large medical institute. This year's virtual experience has been organized in hopes that the medical community continue to connect and share important work on histiocytosis despite travel bans. Efforts will be made to allow participation at the end of each session and again at the end of the meeting with a panel of experienced specialists.

We truly believe with one another's help we will move forward in increasing ECD studies and research, approving treatment options, and aiding in the quality of life for each patient. We are optimistic that you will find the diverse presentations about the ongoing studies, research, and treatments from around the world helpful to your progress in this field.

The medical community's contributions are essential to the success of this organization! The ECD Global Alliance and those it serves are extremely grateful for your involvement and sharing of experiences with others. Please let us know how the organization can best serve you and if you are interested in getting more involved in the work of the organization.

Sincerely,

J. Corkran

Jessica Corkran | *Executive Director*

jessica.corkran@erdheim-chester.org

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ABSTRACTS

Listed in order of presentations.

Kathy Brewer

Erdheim-Chester Disease Global Alliance Achievements and Statistics

ECD Global Alliance, Louisiana, USA

The ECD Global Alliance (ECDGA) has been registering Erdheim-Chester Disease patients since the organization's inception in 2008. Contact information for patients is captured, but little medical information has historically been recorded. The information available provides insight into the number of ECD patients and where they are located. The ECDGA has funded seven research projects and an ECD dedicated patient registry, totaling over $750,000. This has aided effective treatment and mutation discoveries that have drastically improved care for patients. Thirty-five ECD Care Centers have been identified to more effectively provide care to patients across the globe. Support has been provided to over 750 families from 62 countries through the organization's website, events, and more.

Eli L. Diamond, MD

Report on ECD Registry and Analysis of Fatigue and Pain in ECD Registry Patients

Authors:
Anne Reiner,[1] Justin Buthorn,[2] Allison Sigler,[2] Dana Bossert,[2] Thomas Atkinson,[3] Raajit Rampal,[4] Omar Abdel-Wahab,[4] Benjamin Durham,[5] Katherine Panageas,[1] and Eli L. Diamond[2]

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[2] Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, United States (ELD is presenting author)
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Purpose: Erdheim-Chester disease (ECD) is a rare L-group histiocytosis in adults. Patients with ECD endure widely varying and disabling symptomatology including pain and fatigue. The frequency and severity of these symptoms, as well as associated clinical factors, have not been examined in ECD.
Methods: The Memorial Sloan Kettering (MSK) ECD Registry is a prospective longitudinal study of adult patients with ECD. Patients report demographic and treatment characteristics and complete a battery of patient-reported outcomes (PROs), including the Brief Pain Inventory (BPI) and Brief Fatigue Inventory (BFI). PROs are completed at the time of enrollment and at 6, 12, 24, and 36 months. We analyzed fatigue and pain from enrollment PROs. Clinically relevant fatigue or pain was defined as any BPI or BFI item with a score of 4 or more. Recursive partitioning analysis was performed to identify factors associated with clinically relevant fatigue or pain. Spearman correlation was performed to analyze the correlation between pain and fatigue.
Results: 157 patients have enrolled in the ECD registry, 93 from Memorial Sloan Kettering and 64 from other institutions. 148 have completed enrollment PROs, 131 6-month PROs, 118 one-year PROs, and 76 two-year PROs. Clinical data about ECD diagnosis has been fully captured for 115 patients. Fatigue and pain were analyzed for 127 participants. 75 (59%) are male and 52 (41%)

are female. 76 (59%) of patients had been diagnosed with ECD within the past 5 years and 51 (41%) were diagnosed more than 5 years ago. Participants had 0 (14;11%), 1 (38;30%), 2 (36; 28%), and >2 (9; 31) lines of prior therapy. Treatment at the time of PRO completion was conventional in 12 (9%), BRAF or MEK inhibition in 74 (58%) other targeted therapies in 2 (%), and no treatment in 39 (31%). 62 (49%) of participants had moderate or severe (4+) total fatigue score, 60 (48%) had 4+ BRI interference, and 72 (57%) had 4+ fatigue severity. 40 (31%) of participants had moderate or severe (4+) total fatigue score, 41 (32%) had 4+ BRI interference, and 36 (28%) had 4+ fatigue severity. Fatigue and pain severity, interference, and total scores were correlated with one another (correlation coefficients 0.58, 0.53, 0.56; $p<0.001$). Clinically relevant fatigue and pain did not have any association with sites of disease, ECD treatment, or disease status. RPA demonstrated age<70, duration of ECD illness > 9.3 months, and hemoglobin <13 to be associated with clinically relevant pain ($p<0.0001$).
Conclusion: Clinically relevant fatigue and pain are highly frequent in ECD patients, regardless of treatment or disease status. Patients who are younger than 70, with longer duration of ECD illness, and with anemia may benefit from intensive pain evaluation.

BASIC SCIENCE

Giulio Cavalli, MD, Ph.D.

Oncogene-induced maladaptive activation of Trained Immunity in the pathogenesis and treatment of Erdheim-Chester disease

Authors:
Riccardo Biavasco [1]*, Raffaella Molteni [2*,] Davide Stefanoni [2,3,4], Travis Nemkov [3], Jorge Dominguez-Andrs [5], Rob J Arts [5], Ivan Merelli [1,6], Davide Mazza [7], Samuel Zambrano [2,4], Maddalena Panigada [2], Eleonora Cantoni [4], Isak W Tengesdal [5,8], Philippe Maksud [9], Francesco Piras [1,10], Daniela Cesana,[1] Laura Cassina [2], Gianfranco Distefano [2], Alessia Loffreda [7], Daniela Gnani [7], Giacomo De Luca [11], Alessandro Tomelleri [4,11], Corrado Campochiaro [11], Leo AB Joosten [5], Charles A Dinarello [5,8], Anna Kajaste-Rudnitski [1], Julien Haroche [12,13], Simone Cardaci [2], Simone Cenci [2], Lorenzo Dagna [4,11], Claudio Doglioni [4,14], Marina Ferrarini [15], Elisabetta Ferrero [15], Alessandra Boletta [2], Angelo D'Alessandro [3], Eugenio Montini [1], Mihai G Netea [5,16], and Giulio Cavalli [2,4,5,11]

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[13] Centre National de R f rence des Histiocytoses, H pital Piti -Salp tri re, Paris, France, Paris, France.

[14] Department of Pathology, IRCCS San Raffaele Scientific Institute; Vita-Salute San Raffaele University, Milan, Italy.
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Abstract:
We describe a case with synchronic Systemic Aggressive Mastocytosis with Langerhans Cell Histiocytosis in a 55-year-old female, with no response to Midostaurin, Cladribine and after NGS we found a BRAF p.N486_P490del mutation (VAF 38,2%) that is intrinsically resistant to BRAF inhibitor and had a complete response after 2 months of single MEK inhibitor Trametinib.

Jerome Razanamahery, MD

Disturbance of monocyte homeostasis in histiocytosis is close to chronic myelomonocytic leukemia and is correlated with phenotype and disease activity

Authors:
Jerome Razanamahery[1], Maxime Samson[1], Julien Guy[2], Stephanie Francois[3], Jean-Francois Emile[4], Fleur Cohen-Aubart[5], Julien Haroche[5] , Sylvain Audia[1], and Bernard Bonnotte[1]

Institutions:
Dijon University Hospital, Ambroise Paré Hospital, Pitié-Salpétrière Hospital

Abstract:
Purpose: Monocytes have a significant role in histiocytosis pathogenesis. Little is known about their phenotype in histiocytosis and the difference with other myeloproliferative or inflammatory conditions.
Methods: The phenotype of monocytes from patients with histiocytosis was compared to one of the patients with chronic myelocytic monocytic leukemia (CMML), essential thrombocythemia (ET), giant cell arteritis (GCA), and healthy donors (HD). Monocytes were defined as classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{+}CD16^{+}$) and non-classical ($CD14^{+}CD16^{++}$) by flow cytometry analysis.
Results: Seventy-two patients were included (16 histiocytoses, 7 ET, 7 CMML, 21 GCA, and 21 HD). Among histiocytosis patients, eight had ECD among whom five (62.5%) had *BRAF*^{V600E} gene mutation; four patients suffered from LCH among whom one (25%) was *BRAF*^{V600E} mutated. Four patients had RDD among whom two (50%) had *MAP2K1* gene mutation. Three patients with histiocytosis had concomitant myeloid neoplasms (2 CMML, 1 ET), and six had concomitant CHIP. The frequency of classical monocytes was higher in histiocytosis compared to ET (median with IQR: 92% [83.5-96.0] vs 76% [71.0-84.0] for ET. The frequency of intermediate monocytes was lower in histiocytosis compared to ET (4.5% [3.00-7.75] vs 13% [9.00-18.00]) and GCA (4.5% [3.00-7.75] vs 7.91% [6.01-20.75]). The frequencies of classical (87.50% [78.50-92.50] vs 97% [96.0-98.0]), intermediate (5% [4.0-12.25] vs 2.5% [1.250-2.750]), and non-classical monocytes (4% [3.250-11.0] vs 0.5% [0.500-1.500]) differed between CMML patients and patients with both histiocytosis and clonal hematopoiesis. Monocyte subsets were similar between CMML patients and patients with histiocytosis harboring MAP-kinase pathway gene mutation. Monocyte distribution did not differ depending on the type of histiocytosis, molecular status, association with myeloid neoplasms/clonal hematopoiesis, or targeted therapy treatment. The frequency of non-classical monocytes was lower in patients with vascular involvement ([0.775-2.500] vs 4.00% [1.750-9.500]). Intermediate monocytes were less frequent in responder patients (3.5% [2.00-5.00] vs 7.5% [4.00-16.00]).

Conclusion: The distribution of monocyte subsets is homogenous between the different types of histiocytosis. It's close to CMML, a myeloproliferative disorder sometimes involving the MAP-kinase pathway, but different from ET and GCA. Monocyte subset distribution analysis in histiocytosis could be helpful for the diagnosis and be a surrogate marker of disease activity.

Yu Oyama, MD

Novel recurrent mutations in Erdheim-Chester Disease patients identified by whole exome sequencing and whole genome sequencing.

Authors:
Yu Oyama[1] Akira Honda[1], Kensuke Matsuda[1], Hideaki Mizuno[1], Kazuki Taoka[1], Manabu Fujimoto[2], Takashi Ogura[3], and Mineo Kurokawa[1]

Institutions:
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Somatic mutations associated with hyperactivation of MAPK pathway are frequent alterations in patients with Erdheim-Chester disease (ECD), but no known driver mutations are detected in some patients. So far, there is no specific target of treatment for them. To uncover novel driver mutations and establish new treatment strategies in these patients, we performed a nationwide survey and whole-exome sequencing (WES) and whole-genome sequencing (WGS) analysis.

We collected 22 samples of ECD lesions from 15 adult patients. All cases were pathologically proved. A mean of 188 nonsynonymous mutations per patient was identified in tumor-only analysis (range, 17-3598) of WES, and 3134 in tumor-normal analysis (range, 2588-3680) of WGS. We detected known driver mutations in seven of 15 cases (47%). Among them, $BRAF^{V600E}$ was detected in 5 cases, MAP2K1 C121S in 1 case, and NRAS Q61R in 1 case by WES and WGS. The median variant allele frequency (VAF) for these known activating kinase mutations was 14.4% (range, 6.3-34.7). We could not detect known driver mutations in the other 8 cases (53%). Therefore, to reveal novel driver mutations, we focused on these 8 cases. Notably, EPHA2 P786L, MYBPC3 D798N, TDRD5 P115L, and TCEAL4 F17L mutations are recurrently found in 2 out of the 8 cases, and these are not found in the cases with known driver mutations. The VAFs of EPHA2 P786L were 9.1% and 9.3%, MYBPC3 D798N 5.5% and 11.9%, TDRD5 P115L 10.2% and 18.7%, and TCEAL4 F17L 7.5% and 9.0% in each case. In conclusion, we identified EPHA2 P786L, MYBPC3 D798N, TDRD5 P115L, and TCEAL4 F17L mutations as candidates of novel driver mutations in ECD. To elucidate the role of these mutations in the pathogenesis of ECD, further functional analyses are warranted.

ORGAN INVOLVEMENT

Oshrat Rokah, Ph.D.

The Contribution of MicroRNAs to the Inflammatory and Neoplastic Characteristics of Erdheim–Chester Disease

Authors:
Ran Weissman, Eli L. Diamond, Vered Adi Asher-Guz, Julien Haroche, Benjamin H. Durham, Fleur Cohen, Justin Buthorn, Zahir Amoura, Jean-François Emile, Galia Stemer, *Roei D. Mazor, Noam Shomron, Omar I. Abdel-Wahab, *Ofer Shpilberg, and *Oshrat Hershkovitz-Rokah

Instutition:
Assuta Medical Center, Tel-Aviv, Israel

Abstract:
The pathogenesis of histiocytic neoplasms is driven by mutations activating the MAPK/ERK pathway, but little is known about the transcriptional and post-transcriptional alterations involved in these neoplasms. We analyzed microRNA (miRNA) expression in plasma samples and tissue biopsies of Erdheim–Chester disease (ECD) patients. In silico analysis revealed a potential role of miRNAs in regulating gene expression in these neoplasms as compared with healthy controls (HC). NanoString analysis revealed 101 differentially expressed plasma miRNAs in 16 ECD patients as compared with 11 HC, 95% of which were downregulated. MiRNAs-15a-5p, -15b-5p, -21-5p, -107, -221-3p, -320e, -630, and let-7 family miRNAs were further evaluated by qRT-PCR in an extended cohort of 32 ECD patients, seven LCH and 15 HC. Six miRNAs (let-7a, let-7c, miR-15a-5p, miR-15b-5p, miR-107, and miR-630) were highly expressed in LCH plasma and tissue samples as compared with ECD. Pathway enrichment analysis indicated the miRNA contribution to inflammatory and pro-survival signaling pathways. As miR-15a-5p was the most prominently downregulated miRNA in ECD patients compared to healthy individuals we further elucidated its role in ECD pathogenesis. Bioinformatics analysis followed by a luciferase assay showed that chemokine ligand 10 (CXCL10) is a target gene regulated by miRNA-15a-5p. This was confirmed in 24/34 ECD patients that had low expression of miR-15a-5p concurrent with upregulated CXCL10. Overexpression of miR-15a-5p in cell lines harboring BRAF or RAS mutations (Ba/F3, KG-1a, and OCI-AML3) resulted in CXCL10 downregulation, followed by LIN28a and p-ERK signaling downregulation and let-7 family upregulation. Overexpression of miR-15a-5p inhibited cell growth and induced apoptosis by decreasing Bcl-2 and Bcl-xl levels. Finally, treatment of ECD patients with MAPK/ERK signaling inhibitors for 16 weeks resulted in let-7 family members and miR-15a-5p upregulation, which was in parallel with the radiologic response seen by PET-CT. Our study highlights the potential contribution of miRNAs to the inflammatory and neoplastic characteristics of ECD and suggests that miR-15a-5p is a tumor suppressor in ECD through the CXCL10-ERK-LIN28a-let7 axis, highlighting another layer of post-transcriptional regulation in this disease. Also, it suggests that upregulation of miR-15a-5p in ECD patients may have a potential therapeutic role.

CASE STUDIES

Jerome Razanamahery, MD

Dramatic efficacy of Vemurafenib on psychiatric symptoms revealing BRAF^{V600E} Erdheim-Chester Disease

Authors:
ABDALLAHOUI Maroua, RAZANAMAHERY Jérôme, FROMONT Agnès, HAROCHE Julien, IDBAIH Ahmed, CHABRIDON Guillaume, AUDIA Sylvain, BONNOTTE Bernard

Institutions:
Dijon University Hospital

Abstract:
Purpose: Psychiatric manifestations in Erdheim-Chester Disease (ECD) is not described in the spectrum of neurological manifestations, particularly as the initial onset of the disease, making the diagnostic challenging.

Methods: We present the first case of neuro-histiocytosis, presenting as a psychiatric delirium with hallucinations, recovering upon targeted therapy with BRAF ^{V600E} inhibitor.

Results: An 81-year-old Caucasian woman suffered from delirium with hallucination. Her medical history included Grave's disease, deep venous thrombosis, retinal vein occlusion, and macular degeneration. She had auditory hallucinations for 7 months for the current condition, followed by a two-month history of visual hallucinations and logorrhea. She also had persecutory delusion and hallucinations without an underlying psychiatric disorder. The neurological examination showed a cerebellar syndrome (Scale for the assessment and rating of ataxia (SARA) score: 13/40). The patient also had acute heart failure. The echography showed a pericardial effusion requiring drainage. Brain magnetic resonance imaging (MRI) showed confluent FLAIR hyperintensity lesions in the pons and superior cerebellum peduncles. Lumbar puncture was unremarkable except for elevated neopterin. Body computed tomography showed a "hairy kidney" and adventitia vessels thickening. The 18 fluorodeoxyglucose PET showed bilateral symmetric osteosclerosis of long bone suggestive of ECD. The diagnostic was confirmed with a perirenal biopsy showing diffuse infiltration of CD68+, CD1a- histiocytes with BRAF ^{V600E} gene mutation on pyrosequencing. The patient received interferon-alpha (180 micrograms/week) twice then specific BRAF inhibitor Vemurafenib. Rapid regression of the psychiatric symptoms and neurological improvement (SARA Score: 12/40) occurred within days of treatment. After 8 weeks, the patient had clinical improvement. The brain MRI showed partial regression of the lesions. 18FDG-PET shows a reduction in radiotracer uptake on all ECD sites compatible with a partial metabolic response.

Conclusion: This case highlights the first description of delirium as a manifestation of neuro-ECD with dramatic improvement with targeted therapy.

André Neder Ramires Abdo, MD

Synchronic Systemic Aggressive Mastocytosis and Langerhans Cell Histiocytosis with BRAF p.N486_P490del

Authors:
Otavio Baiocchi, Philip Bachour, and Jean Francois Emile

Institutions:
Oncology Center at Hospital Alemão Oswaldo Cruz, São Paulo

Abstract:
We describe a case with synchronic Systemic Aggressive Mastocytosis with Langerhans Cell Histiocytosis in a 55-year-old female, with no response to Midostaurin, Cladribine and after NGS we found a BRAF p.N486_P490del mutation (VAF 38,2%) that is intrinsically resistant to BRAF inhibitor and had a complete response after 2 months of single MEK inhibitor Trametinib.

ORGAN INVOLVEMENT

Anaïs Roeser, MD

Role of vascular endothelial growth factor in Erdheim-Chester Disease

Authors:
Anaïs Roeser, MD, Marine Bravetti, MD, Lida Dong, MD, Levi Dan Azoulay, MD, Makoto Miyara, MD, Jean François Emile, MD, Ph.D., Frederic Charlotte, MD, Ph.D., Isabelle Brocheriou, MD, Ph.D., Zahir Amoura, MD, MSc, Fleur Cohen Aubart, MD, Ph.D., and Julien Haroche, MD, Ph.D.

Instutition:
Assistance Publique Hôpitaux de Paris

Abstract:
Erdheim-Chester disease (ECD) is a rare histiocytosis characterized by tissue infiltration of CD68+, CD1a- histiocytes, derived from cells of the mononuclear phagocyte system harboring recurrent mutations in the MAPK-signaling pathway. Vascular endothelial growth factor-A (VEGF-A), also referred to as VEGF, is a major regulator of angiogenesis. In Mycobacterial-associated granulomas, macrophages produce VEGF that induces the recruitment of monocytes. VEGF is expressed by histiocytes in Langerhans cell histiocytosis. We hypothesized that VEGF could play a role in ECD pathophysiology. The first aim of our study was to determine if VEGF was expressed by histiocytes in ECD lesions. The second aim was to assess levels of serum VEGF (sVEGF) in ECD patients, and determine if they were associated with the patient's characteristics.

We conducted a retrospective study, screening all ECD patients seen in the French National Reference Center for Histiocytoses of the Pitié-Salpêtrière Hospital from 2009 to 2019. Patients were included if they had at least one sVEGF determination. Biopsies of patients with extreme sVEGF were centrally reviewed and stained for VEGF with 2 different antibodies.

We included 248 patients in the analysis. sVEGF were high (> 500pg/mL) at first determination in 53%. Median sVEGF was 843pg/mL in the high sVEGF group, 288pg/mL in the low sVEGF group. Sex, age, and BRAF status were not significantly different between the 2 groups. We analyzed 26 histological samples of ECD. Histiocytes had moderate to high VEGF staining in all samples

analyzed. Control included 4 biopsies of reactional sinusal histiocytoses, in which no VEGF staining was observed on histiocytes. Patients with high sVEGF had more frequently a vascular involvement (71% vs 48%, p=0.0004), especially a “coated aorta” (50% vs 34%, p=0.009), and a cardiac involvement (58% vs 41%, p=0.008). Consecutive measurements of sVEGF were available for 183 patients (median interval: 24 months). sVEGF significantly decreased during follow-up (p<0.0001), with a median variation (ΔsVEGF) of -153pg/mL. Consecutive cardiac MRIs were available for 45 patients (median interval: 48 months). Thoracic aorta coating was present in 31 patients (69%) and persisted in all cases. All patients had cardiac involvement: 6 achieved complete response, 25 partial response, 12 were stable, and 2 progressed. Mean ΔsVEGF of patients with complete response, partial response, stable disease were respectively - 591.3, - 163.9, - 239.6pg/mL and were significantly different from patients who progressed (mean ΔsVEGF + 555.5pg/mL).

In our study, VEGF was expressed by ECD histiocytes. sVEGF was high in 53% of ECD patients, and its elevation was associated with cardiac and vascular involvements. Variations of sVEGF were associated with responses of cardiac involvement under therapy.

Francesco Pegoraro, MD

Kidney involvement in Erdheim-Chester disease: a multicenter cohort study on 195 patients

Authors:
Francesco Pegoraro, Thibaud Chazal, Gaia Manari, Valerio Maniscalco, Elena Gelain, Alessandra Bettiol, Frederic Charlotte, Roei D. Mazor, Hassan Izzedine, Augusto Vaglio, Julien Haroche

Institution:
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Abstract:
Background: Erdheim-Chester disease (ECD), a non-Langerhans cell histiocytosis, infiltrates the peri-renal retroperitoneum in around 60% of cases and often causes obstructive uropathy. Little is known about kidney function and prognosis in ECD. Herein, we investigated kidney involvement and outcome in a large cohort of ECD patients.

Methods: Consecutive patients with histologically confirmed ECD followed at four referral centers in France, Italy, and Israel between 2000-2020 were included. Data on kidney function were assessed at diagnosis and last visit; where available, data collected at one, two, and five years, were also included. Imaging studies and information on medications and responses to treatment were collected.

Results: One hundred and ninety-five patients (72% of whom were men) were included (mean age at onset 52±15.5 years; mean age at diagnosis 56.5±14.3 years). Perirenal involvement was found in 142 patients (73%). Of them, 81 (42%) also had ureteral involvement, 74 (38%) hydronephrosis, 16 (8%) kidney atrophy, 60 (31%) vascular peduncle, and 37 (19%) adrenal gland involvement. Perirenal involvement was significantly associated with older age (p=0.001), male sex (p=0.004), hypertension (p=0.001), large vessel (p25% and ESKD/death at last visit were an age at onset >50y, hypertension, the $BRAF^{V600E}$ mutation, and a low eGFR at baseline. At multivariate analysis, the presence of cardiovascular risk factors was significantly associated with CKD 4-5 or eGFR decrease >25% (p=0.005), whereas age >50y was associated with ESKD or death (p=0.005). Interestingly, conventional therapies (e.g., interferon- α, anti-cytokine drugs) had a

protective effect on the risk of ESKD or death (p=0.029).

Conclusions: Perirenal infiltration is frequent in ECD and is associated with worse renal function at the time of diagnosis; however, cardiovascular risk factors and age are the main independent predictors of kidney outcome.

TREATMENTS

Ashley Aaroe, MD

Treatment of Non-Langerhans Cell Histiocytosis with the MEK Inhibitor Trametinib

Authors:
Razelle Kurzrock MD, Gaurav Goyal MD, Aaron Goodman MD, Harsh Patel MD, Gordon Ruan MD, Gary Ulaner MD Ph.D., Jason Young MD, Ziyi Li, Derek Dustin, Ronald Go MD, Eli Diamond MD, Filip Janku MD Ph.D.

Institutions:
MD Anderson Cancer Center

Abstract:
Erdheim-Chester disease (ECD) and Rosai-Dorfman disease (RDD) are rare non-Langerhans cell histiocytoses with limited therapeutic options. Recent studies suggested that activation of the MAPK pathway through $BRAF^{V600E}$ mutation or other alterations is a hallmark of histiocytosis and can be associated with a favorable response to BRAF inhibitors or the MEK inhibitor cobimetinib. To assess efficacy and safety, we analyzed 26 real-world patients (17 ECD, 5 ECD/RDD, 3 RDD, 1 ECD/LCH) treated with the oral MEK inhibitor trametinib at four major US care centers. Most patients were effectively managed at reduced doses of 0.5mg to 1 mg of oral trametinib daily. The most common treatment-related toxicity was rash (27% of patients). The response rate in evaluable patients was 71%. At the median follow-up of 23 months, treatment effects were durable with a median time-to-treatment failure of 37 months while median progression-free and overall survival have not been reached.

Eli L. Diamond, MD

Outcomes after discontinuing targeted therapy in ECD and other histiocytoses

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Abstract:
Purpose: There is data to suggest that interruption of BRAF inhibition in patients with Erdheim-Chester Disease frequently leads to disease relapse. In this study, we present outcomes in diverse histiocytosis patients treated with BRAF, MEK, or dual BRAF/MEK inhibition, with subsequent treatment interruption. Methods: Patients with Erdheim-Chester disease (ECD), Langerhans cell histiocytosis (LCH), Rosai-Dorfman disease (RDD), Juvenile Xanthogranuloma (JXG), or mixed histiocytosis (ECD/LCH or ECD/RDD) whose targeted therapy was interrupted in favor of observation or chemotherapy were analyzed for subsequent relapse and recaptured response after rechallenge with targeted therapy. Relapse-free survival (RFS) was calculated from the date of treatment interruption until relapse (n=14) for those with an event or until last follow-up for those who were censored (n=6). There were no patients who died without relapse. Histiocytosis subtypes, duration of treatment and disease status prior to treatment interruption, tumor mutation, and class of targeted therapy were associated with RFS using Cox proportional hazards modeling. Results: 20 patients were analyzed. 13 (65%) were male, and diagnoses were ECD (8; 40%), ECD/LCH (4;20%), LCH (2;10%), RDD (2;10%), ECD/RDD (2;10%), and JXG (2;10%). Patients were initially treated with BRAF inhibition (9; 45%), MEK inhibition (9;45%), or dual therapy (2; 10%), and at the time of treatment interruption 13 (65%) had a complete response (CR) and 7 (35%) had a partial response (PR). Following treatment interruption, 14 (70%) of patients had subsequent relapse at a mean time of 9.7 months; 13 of these were rechallenged, and 9 (of 10 evaluable) recaptured a CR or PR. The 6 patients who did not relapse had ECD or mixed disease (3), JXG (2), and RDD (1); 5 of these 6 were treated with MEK inhibition prior to interruption, and the 6th with dual therapy. Patients with BRAFV600E mutation (HR: 6.1; 95%CI: 1.3-27.9) or BRAF inhibitor monotherapy (HR: 3.3; 95%CI: 1.0-10.0) were more likely to relapse. Conclusion: Relapse following interruption of targeted therapy is frequent in histiocytosis. Further study may demonstrate patients with less frequent relapse, such as those with non-ECD disease treated with MEK inhibition.

INERNATIONAL UPDATES

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Thank you for your attendance and participation!

You will be receiving a follow-up email including the following:

- A list of open ECD trials and studies
- New Pathology Guide: An Algorithmic Approach to a Diagnosis
- Registration & details for 2022 event
- The recording of this meeting