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THE FUTURE OF CASTLEMAN DISEASE RESEARCH: PROCEEDINGS FROM 2015 AND 2016 ANNUAL MEETINGS

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ABSTRACT

Castleman disease (CD) describes a rare, heterogeneous group of lymphoproliferative disorders that share common histopathological lymph node features. CD affects individuals of any age and can be fatal if not accurately diagnosed and adequately treated early in its course. The Castleman Disease Collaborative Network (CDCN) is a global network launched in 2012 to raise awareness and accelerate research for Castleman disease. This proceedings paper describes the 2015 and 2016 CDCN Annual Meetings, highlights the progress that has been made, and outlines future directions. At the end of each year, there is a Patient & Loved Ones Summit, a Physicians & Researchers Meeting, and a Scientific Advisory Board Meeting. Important developments at these meetings and throughout the year include connecting new patients, confirming the contents of the first-ever diagnostic criteria for one sub-type of CD, and prioritizing the international CD research agenda. Meetings such as these are of paramount importance to develop and advance the research agenda of small orphan disease research organizations. These meetings help the CDCN to promote international collaboration, incorporate patient perspectives, maintain a focused agenda, and, importantly, serve as a model for other rare disease research foundations. In the year that passed between the 2015 and 2016 meetings, the CDCN had its most successful year, with incredible strives being made in cutting edge research, physician and research education, and patient support.

BACKGROUND

Castleman disease (CD) describes a group of three rare and heterogeneous lymphoproliferative disorders that share common histopathological features. CD can occur in a single region of enlarged lymph nodes, which is referred to as unicentric CD (UCD), and in multiple regions of enlarged lymph nodes, which is referred to as multicentric CD (MCD). MCD patients experience flu-like symptoms, fluid accumulation, cytopenias, and multiple organ system dysfunction due to a cytokine storm often including interleukin (IL)-6. A subset of MCD is caused by human herpesvirus-8 (HHV-8) and is termed HHV-8-associated MCD. The remaining cases are idiopathic in origin and termed HHV-8-negative or idiopathic MCD (iMCD). iMCD is particularly poorly understood by the medical community.[1] There are an estimated 6,500–7,700 CD cases/year in the USA with about 1,650 cases of MCD.[2] Historically, 35% of MCD patients die within 5 years of diagnosis and 60% die within 10 years.[3] Over 20 different treatments have been reported for iMCD with variable effectiveness, and there is only one FDA-approved therapy. [4]

The Castleman Disease Collaborative Network (CDCN) is a global initiative dedicated to accelerating research and discovering treatments for CD.[5] On December 4-6, 2015, the CDCN held an Annual Meeting in Orlando, FL as a satellite of the 2015 American Society of Hematology (ASH) meeting. The three-day conference consisted of a Patients & Loved Ones Summit, a Physicians & Researchers dinner meeting, and a Scientific Advisory Board meeting. The CDCN held similar meetings in the final quarter of 2016. Key highlights for 2015 and 2016 are listed in **Tables 1 and 2**, respectively.

PATIENTS & LOVED ONES SUMMIT

The CDCN's second annual Patients & Loved Ones Summit, "Beating Castleman's, Together," held in December 2015, provided an opportunity for patients and loved ones from around the world to (1) connect with one another, (2) learn about their disease and the latest research, (3) contribute research ideas and patient priorities, and (4) discover ways in which they could join the fight to advance research and treatments for CD. Twenty-six patients and loved ones from across the

Table 1. Key Take-Aways from 2015 Annual Meetings
Over the course of the three-day meeting, the CDCN organized several speakers, awards, and patient events to celebrate the year-end progress of the organization. This table highlights key points that we consider to be milestones for Castleman disease research and awareness efforts in 2015.

• For many patients in attendance, the Patient & Loved Ones Summit was their first time meeting someone else living with their disease.
• The 2015 Jim Johnston Castleman Warrior Award was given to Kim Driscoll, the mother of a pediatric Castleman patient who passed away in 2014. Kim has continued her daughter's fight against Castleman disease in various ways including providing regular support to other patients and loved ones and organizing annual motorcycle rides to raise funds for Castleman disease research.
• Over 50 hematologists/oncologists, pathologists, physician-scientists, translational researchers, and pharmaceutical partners attended the fourth annual Physicians & Researchers meeting, "Accelerating Research & Treatments for Castleman Disease".
• Planning began for the launch of the first Castleman disease patient registry and natural history study, known as ACCELERATE. The study combines data from physicians and patients around the world to better understand Castleman disease and facilitate future research in order to provide insights into diagnosis, treatment, and outcomes.
• In November 2015, the CDCN established the first-ever diagnostic criteria for Castleman disease. One month later at the SAB meeting, the criteria were refined to more effectively rule in patients and adequately define Castleman disease as a clinical syndrome.

Table 2. Key Take-Aways from 2016 Annual Meetings
This table highlights key points that we consider to be milestones for Castleman disease research and awareness efforts in 2016.

• The 2016 Patient and Loved Ones Summit had over 50 attendees.
• The 2016 Jim Johnston Castleman Warrior Award was given to Gary Gravina, a patient with a severe subtype of Castleman disease called idiopathic multicentric Castleman disease (iMCD) with TAFRO syndrome. In addition to overcoming two life-threatening episodes, Gary frequently contributed blood and tissue samples to research. His family also contributed funds to enable essential research studies.
• Over 50 hematologists/oncologists, pathologists, physician-scientists, translational researchers, and pharmaceutical partners attended the fifth annual Physicians & Researchers meeting, "Accelerating Research & Treatments for Castleman Disease".
• The ACCELERATE Registry began enrollment in the United States and Europe in 2016.
• The diagnostic criteria that the CDCN spearheaded was submitted and accepted for publication in 2016.

United States as well as the Netherlands and Switzerland were in attendance. For many of the patients, this was their first time meeting another patient with their disease. The Summit began with the attendees introducing themselves and sharing their often emotional experiences battling CD. Representatives from the CDCN then gave presentations that focused on two major themes: (1) the current state of knowledge and research on CD and (2) methods through which patients and loved ones can become "Castleman Warriors"—a title given to individuals committed to raising awareness and funds for CD—to help advance the search for a cure. One of the more somber moments of the Summit came during the viewing of "Teal," a film about a 13-year-old girl who passed away from CD. The film highlighted that misdiagnoses and inappropriate treatment regimens can lead to fatal outcomes and emphasized the importance of the CDCN's mission to push forward both research and awareness. The film also served as an important example of how the loved ones of patients affected by CD are fighting back; it was made by a cousin of the patient in the film and will continue to be a powerful tool to raise awareness.

Following a reception and dinner, the evening sessions commenced with the presentation of the second annual Jim Johnston Castleman Warrior Award. This award is given in recognition of the time and energy that the selected winner has dedicated to advancing the Castleman Warrior cause and providing support to other patients and loved ones along the way. The 2015 award was given to Kim Driscoll, the mother of a pediatric CD patient who passed away in 2014. Kim has continued her daughter's fight against CD in various ways and has been one of the CDCN's most active volunteers.

The Summit closed with an open question and answer session with a panel of expert CD physicians and researchers including Drs. Frits van Rhee, Kazuyuki Yoshizaki, David Fajgenbaum, and Jason Ruth. The panel addressed the questions and concerns of the attendees and provided further insight into future research plans and emerging treatment options. In summary, the Summit was the largest CD patient meeting, generated important concepts for future research, and contributed vital information to the community of patients and their loved ones, physicians, and researchers.

PHYSICIANS & RESEARCHERS MEETING

The fourth annual Physicians & Researchers dinner meeting, titled "Accelerating Research & Treatments for Castleman Disease," took place on the evening of December 5, 2015. The objectives of the meeting were to (1) define the current state of research on pathogenesis, diagnosis, and treatment of CD, (2) discuss priorities to advance research and improve patient care, (3) gain insights from clinicians and researchers about opportunities for progress, and (4) determine key action steps for the CDCN, clinicians, and researchers to uncover the pathogenesis of iMCD. Over 50 hematologists/ oncologists, pathologists, physician-scientists, translational researchers, and pharmaceutical partners attended. Dr. Fajgenbaum, Executive Director of the CDCN, opened the meeting with a session on the current state of knowledge for CD. He reviewed the three subtypes and provided the most up-to-date information on the disease's clinical features, treatment regimens, and outcomes. Dr. Fajgenbaum went on to reveal the details of his own experience battling CD as a patient prior to becoming a physician-researcher. He concluded his talk by highlighting a new model of CD pathogenesis, which he proposed in 2014,[1] and the key areas for future research.

Dr. Thomas Uldrick, Senior Clinician at the National Cancer Institute of the National Institutes of Health, presented the other diseases that must be ruled out before making the diagnosis of iMCD. The presentation allowed for additional contributions and evaluations from the attendees. Dr. Fajgenbaum gave the final presentation on the current state of CD research and the CDCN's comprehensive research agenda. He outlined the organization's vision for elucidating a diagnostic biomarker, understanding the etio-pathogenesis, and discovering new treatment targets to identify an effective therapy for each subtype of CD.

The meeting segued into its final agenda item, a small group discussion and open forum on a variety of topics. Attendees were asked to discuss the following questions in their groups: (1) What research questions, if answered, would be most helpful for your patients? (2) How can we promote collaborations to answer these questions? (3) Have you used new treatments or made any interesting clinical observations? (4) What should be our top patient support priorities for 2016? (5) What do you plan to do to advance iMCD research or patient care after this meeting? The diverse group of attendees touched on many topics and set the stage for continued collaboration. The information that was gathered from the session helped to prioritize research objectives going

forward. The meeting concluded with an invitation for physicians and researchers to join the fight against CD by applying for CDCN-funded research grants, contributing tissue samples to research, publishing their case reports, and participating in the global CDCN research community.

SCIENTIFIC ADVISORY BOARD MEETING

The CDCN concluded its three-day conference with its fourth annual Scientific Advisory Board (SAB) meeting on December 6, 2015. The CDCN SAB was initially assembled in 2012 to connect the top global experts on CD in order to set the overall direction and priorities of the organization. Currently, the SAB includes 32 members representing eight countries, including the United Kingdom, United States of America, Brazil, Norway, Japan, France, New Zealand, and China. The attendees came together to discuss both the progress made in 2015 and the direction and hopes for the organization in 2016. The discussion specifically focused on (1) the patient registry and natural history study, (2) updates and future plans for the international research agenda, and (3) the proposed diagnostic criteria for iMCD.

The patient registry and natural history study, known as ACCELERATE, is an observational, web-based study that combines data from physicians and patients around the world to better understand CD and to facilitate future research. During this meeting, the SAB discussed operational hurdles that needed to be overcome for ACCELERATE to move forward successfully. The SAB reviewed the impact, funding, and status of several other CDCN studies. Preliminary results were presented, feedback from key researchers was incorporated, and opportunities for further collaboration were discussed.

Deliberations shifted to the diagnostic criteria of iMCD, which has been established during the International Castleman Disease Diagnostic Criteria Meeting held in November 2015. SAB members who attended the criteria meeting presented the rationale for the inclusion of specific clinical and laboratory features, and members who were not present at the original meeting were able to provide feedback. This led to refinement of the diagnostic criteria, which the CDCN believes will help physicians to make more timely diagnoses and administer appropriate treatment regimens to patients.

ONE-YEAR FORWARD: PROGRESS IN 2016 AND PLANS FOR THE FUTURE

The 5th Annual Meeting of the CDCN was held over December 3-4, 2016 in San Diego, CA, again as a satellite meeting of the ASH annual conference. Many of the attendees from the previous year, as well as new attendees, convened to hear presentations on the progress over the past year as well as the plans for 2017. Overall in 2016, ten high-impact research studies were launched, with two still in process, thanks to a three-fold increase in available funding in 2016 compared to what was available to the CDCN in 2015. These studies include a study conducted through Columbia University in search of a causative pathogen, whole genome sequencing, serum proteomics studies, and very importantly, our international patient registry and natural history study, ACCELERATE. The ACCELERATE registry was officially launched in 2016 and is currently enrolling patients in the United States and in Europe, and hopefully will be able to expand to other areas of the world as well. The registry is also aiding in the procurement of critical patient samples to be stored and used for future research. These samples can now be housed in one, central Castleman disease BioBank, which is set to launch publicly in 2017.

Beyond these research studies, many other important advances have been made in regards to how CD is diagnosed, described, and spoken about, between researchers and physicians as well as among patients. The third annual Patient Summit was held in Philadelphia, PA on November 4, 2016. Over 50 patients and their loved ones traveled from across the US as well as from Germany, Japan and Australia. During this two-day event, patients were spotlighted, new research developments were described, and vital sample donations were obtained. In conjunction with the Patient Summit, CDCN hosted its largest fundraiser of the year, the “Quest for a Cure” Gala, on the evening of November 4. Castleman disease received its first ever, unique ICD-10 code in October of 2016, allowing for easier identification of a patient with the disease and separating CD within medical records from many other, unrelated disease entities. Lastly, the first ever diagnostic criteria, described earlier as a main point of conversation from the 2015 CDCN Annual Meeting, was finalized and accepted for publication by *Blood* in December 2016.[6] This publication is a milestone accomplishment for the CDCN, as the criteria, which were established through international consensus based on evidence from over 200 patients, will help to increase the rate and accuracy of CD diagnosis.

Like 2015, 2016 surpassed previous years with regards to scientific progress. This success in the rare disease sector is due to the unique structure we have built at the CDCN. Our interactions with patients and loved ones have

created a powerful force of advocacy and a network for sample donations, our expansive physician and researcher network continues to grow around the world, and our prioritized research agenda is pushing forward high-impact studies that have never before been investigated in Castleman disease. At the conclusion of our 2016 Annual Meeting, we posed the same questions to the Physicians & Researchers meeting as we did in 2015; the proposed plans for 2017 are found in **Table 3.**

CONCLUSION

The Annual Meetings of the CDCN are important opportunities for our international network to come together to learn of new developments and to prioritize goals for the upcoming year. Between the 2015 Meeting, described above, and the 2016 Meeting, we launched several research studies that were prioritized into an International Research Agenda, obtained and distributed more research funding than ever before, launched an international patient registry, and published the first-ever diagnostic criteria. These meetings are essential to the CDCN's efforts to foster collaboration, increase patient and community engagement, and execute a prioritized international research agenda. The CDCN's approach can serve as a model for other rare disease organizations to follow in order to foster increased awareness and to optimize engagement of the community of researchers and clinicians around the world. Global collaboration is

Table 3. Proposed Plans from 2016 Annual Meetings

The five questions below were posed to the audience at the conclusion of the 2016 Physicians and Researchers meeting. Key responses from group members are included here to show highlights of the research and patient-centered agendas for the coming year.

What research questions, if answered, would be most helpful for your patients? Participants proposed that the Castleman disease community search for diagnostic biomarkers, expand information to non-English speaking physicians and patients, and educate community pathologists on the new diagnostic criteria.
How can we promote collaborations to answer these research questions? Participants suggested that the CDCN continue to host forums such as the annual meetings to increase international collaboration, incentivize sample donation to the BioBank, have clear instructions on how to donate samples to the CDCN BioBank ("CastleBank"), and get IRB approvals to allow for procurement of samples during disease flares.
Have you used new treatments or made any interpreting clinical observations? Participants shared that while anti-IL-6 treatment remains a mainstay, treatment options for non-responders include combination chemotherapy, anti-IL1 (anakinra), and immunosuppressants/ immunomodulators like sirolimus, cyclosporin, bortezomib, thalidomide, and lenalidomide. Anti-VEGF therapy and treatments targeting the JAK-STAT pathway were also proposed. The role of stem cell transplant was also discussed for non-responders.
What should be our top patient support priorities for 2017? Participants suggested that key priorities for 2017 include: 1) extending the CDCN's physician network and participation, especially in the age of electronic information, to lessen the burden on patients seeking care, 2) expanding our information and registry beyond the English language, 3) enrolling as many patients as possible in the registry, and 4) performing whole genome sequencing, lymph node tissue studies, and proteomics studies.
What do you plan to do to advance MCD research or patient care after this meeting? Participants committed to initiating new retrospective studies in their respective countries, creating programs to better train pathologists in diagnosis, collaborating to find large scale ways to identify biomarkers in patients' serum.

essential for rare diseases that are poorly understood, underfunded, and have disparate researchers.[7]

AUTHORS' CONTRIBUTIONS

MC and RJ wrote the manuscript. All authors read and reviewed the final version of the manuscript.

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