In a world that has 7,000 known rare diseases, with only 5% having any treatment available, the future of discovery and new treatment development in cutaneous lymphoma is promising. There is much hope for a brighter future for everyone living with this condition.

Beginning with the 3rd World Congress of Cutaneous Lymphomas held in October, 2016, the diverse global community of cutaneous lymphoma has come together at three unique scientific meetings to discuss and share the most recent discoveries and research covering all aspects of this complex, rare disease. From the laboratory where scientists test theories about how the disease works to new treatment combinations being used in the clinic, the pace of discovery has been moving fast.

The CLF team had the privilege of attending these meetings over the last several months with the goal of capturing major highlights to share with our community.

MEETING HIGHLIGHTS

3rd World Congress of Cutaneous Lymphomas, October 26-28, NYC

Over 400 participants from all over the world convened on the campus of Columbia University in late October bringing together the largest scientific meeting dedicated to cutaneous lymphoma to date. This multinational meeting showcased 160 abstract posters and over 100 oral presentations over the course of the three-day program. All specialties were represented - dermatology, hematology/oncology, pathology, nurses, physician assistants, laboratory researchers and many others. Updates on immunology and therapy were presented. And for the first time, a session dedicated to quality-of-life to discuss the impact of non-clinical issues like access to experts, cost of treatments, and availability of treatment on patients. Although the oral presentations were short, 8-9 minutes long with a few minutes for questions, the networking and collaboration that occurred throughout the meeting showed the commitment and passion of this incredible group of people who have dedicated their time, energy and careers to helping patients. From a patient perspective, it was inspiring.

Dr. Steven Swerdlow, Professor of Pathology and Director of the Division of Hematopathology at the University of Pittsburgh Medical Center, kicked-off the conference with a presentation on the history of cutaneous lymphoma classifications. The first global consensus of classifications was published in 2006 by the World Health Organization, not that long ago. Updates and revisions continue to be made in collaboration with global clinical advisory committees. Why are these global disease classifications important? As the knowledge continues to deepen and grow about the variations of the different types of cutaneous lymphomas, the classifications continue to expand or be enhanced which provides clinicians a better framework for diagnosing and treating patients. This keynote presentation set the stage for the robust program that followed.
Updates on Subtypes

**Mycosis Fungoides (MF):**

Mycosis fungoides is the most common of all cutaneous lymphomas and presents with a wide range of initial disease that may or may not evolve over time. Early stage disease is challenging to diagnose for a number of reasons and biomarkers as indicators of later progression have not yet been identified. Studies into the initial biopsies of MF patients appear to differ between diseases with a long stable course and those with progression. Further exploration is required to determine whether higher expression of distinct biomarkers in early disease stages might be a relevant contributive factor to progression of disease in MF patients. These markers could be future potential diagnostic indicators.

The landscape of cutaneous lymphoma mutations is complex. Unfortunately, there are no single targets for the vast majority of patients. Epigenetic differences arise during the lifetime of all people. It is challenging to determine what is related to the disease and what a natural change due to time and age is. However, research into these epigenetic changes shows promise. In MF, the STAT3 pathway appears to be important. The miR-124/epigenetic cell regulatory system is known to regulate the STAT3 pathway. For some reason, the regulatory function is silenced in MF tumor stage. This could be a potential pathway for targeted therapy development.

Lack of highly specific markers for malignant lymphocytes prevents early diagnosis of MF and timely treatment. Studying the role of the IL-13 protein and its signaling molecules suggest it may act as a growth factor for these cells in MF. This could prove to be a novel molecular marker for cutaneous lymphoma malignancy and potentially represent markers for early diagnosis as well as a potential therapeutic target for treatment.

Studies were presented that reviewed the importance of the IL-10 immunoregulatory cytokine (a small molecule protein that is important in cell signaling) in the progression of MF. IL-10 was detected in all stages of MF and increasing levels were found as the stage of the disease progressed. The laboratory studies confirmed that the IL-10 pathway could be considered as a potential target for treating advanced disease by developing an antibody that interrupts the growth of the cancer cells.

**Folliculotropic MF (FMF):**

Data presented based upon a large cohort of patients reported:
- Two distinct variations of FMF, each has a distinctive clinical pathological pattern;
- Very different prognosis depending upon which variant (slow growing versus more aggressive) and appears to be in alignment with prognosis for classic MF;
- FMF occurs in less than 10% of the cutaneous lymphoma patient population;
- The epicenter for FMF is deeper than in classic MF;
• More aggressive (advanced stage) is less responsive to standard skin-directed therapies. Better responses were seen in this group of patients when using local radiotherapy, total skin electron beam or PUVA combined with local radiotherapy;
• Slower growing (early stage) patients benefit from non-aggressive, standard skin-directed therapies similar to classic MF (single therapy of topical steroids, UVB and PUVA). PUVA may be more effective as a single therapy for early stage FMF. However, it was found that a higher number of treatments are needed to achieve a response than when used for treatment of classic MF;
• Additional studies of this subtype are recommended to expand the understanding of the differences and potential treatment pathways.

Large Cell Transformation in Mycosis Fungoides:

There is general agreement that there is a poor prognosis for patients with large cell transformed MF, but not every person has a poor prognosis. The challenge is to predict who will do better. Unfavorable prognostic factors appear to correlate with lower survival. Having two or more key risk factors equates to higher risk for progression. The risk factors from a number of studies are reported as:
  • Loss of CD8
  • Loss of CDKN2A/2B
  • Negative staining for CD30
  • Extent of skin lesions showing transformation
  • Transformation at extra cutaneous sites

Recommended for future research to confirm prognostic factors for large cell transformed MF is the inclusion of only cases confirmed by pathologic review in prospective studies.

Primary Cutaneous Aggressive CD8+ Epidermotropic T-cell (PCAETCL)

This is a very rare, aggressive and poorly understood variant of cutaneous lymphoma. This variant appears to be more prevalent in men and many patients have had chronic lesions for a long time. Some have diagnosis of MF or other skin diseases like psoriasis, etc. It has a poor and short response to chemotherapy (single or combo). Allogeneic stem cell transplantation provided the best option for long-term remission. More research is needed to gain a better understanding of this subtype.

CD8+ Mycosis Fungoides

An uncommon variant observed most often in younger patients. Hypo-pigmented presentation of skin lesions are more common in patients with dark complexions. Most patients achieved complete responses to treatments, however relapse was observed in 33%. Based upon the
retrospective review of cases, it was concluded the CD8+MF has an indolent (slow) course and skin directed therapies are the preferred treatment approach.

**Unilesional Mycosis Fungoides**

This rare variant of MF typically appears as a solitary lesion, indistinguishable clinically and histopathology from patch/plaque MF. This variant appears to have an excellent prognosis with no recurrence and shows a different immune marker profile than classic MF. Additional studies are required to validate the link, but these immune markers could be potential diagnostic indicators for differentiating this type of MF, targeting treatment for this variant and monitoring for progression.

**Pediatric Mycosis Fungoides**

There is sparse information available about MF in the pediatric population. Hypo-pigmented MF seems to be more prevalent in this age group. Interestingly, the study found that FMF is not uncommon in children and adolescents. The development of MF is generally poorly understood, especially in a younger population. In this population of patients, the main presentations of cutaneous lymphoma were hypo-pigmented, folliculotropic and classical MF with early stage disease. Some patients had a combination of the different variants, some only one variant. Most patients achieved a complete response with phototherapy as a monotherapy. In this patient population, phototherapy appears to be effective for those with FMF as well. Based on this study, pediatric MF in general follows a more slow-growing course than MF in adults. The study suggests that pediatric MF as a group differs from its adult counterpart and may have a different patho-immunogenetic root. Additional research into this patient population is needed to gain a better understanding of prognosis, treatment impact and long-term disease history.

**Sézary Syndrome (SS)**

PLCG1 has been identified as a mediator of T-cell receptor signaling and is a highly mutated gene in cutaneous lymphoma. Studies investigating the importance of this signaling in Sézary Syndrome showed that PLCG1 may represent novel therapeutic targets for small molecule inhibitors. These inhibitors target this pathway alteration and the disease manifestation of Sézary Syndrome. Future work will focus on reproducing these findings with the ultimate aim of assisting the bench-to-bedside approach to producing targeted therapies with small molecule inhibitors focused on the PLCG1 irregularities in SS.

TOX (Thymocyte selection-associated HMG bOX) is a gene family that plays a role in regulation of the immune system. This gene is modified in Sézary Syndrome by showing an increase in the proteins on the cell surface. It was determined in a study that this modification in SS can lead to changes in expression of other genes related to disease development and progression. This is not seen in psoriasis and appears to have an impact in both MF and SS. Additional studies should be explored, including investigating how romidepsin (Istodax is the
brand name) works in treating SS. Understanding this mechanism of action could provide additional insights into what treatment to use when for which patient.

Sézary Syndrome disease development is still poorly understood, but chronic antigen stimulation due to a bacterial or viral infection or colonization of the skin may lead to malignant transformation of the skin resident T-cells. Re-evaluation of the long standing premises that viruses play a role in cutaneous lymphoma was investigated using new technology. The origin or cause of cutaneous lymphoma remains unknown, although many hypotheses have been put forward that occupational exposures or infectious agents may play a role. Cutaneous lymphomas are known to have a connection with suppression of the immune system which can lead to overwhelming infections which might implicate viral agents. All efforts to confirm the impact of viruses have not shown consistent results. A novel and highly sensitive viral detection technique (VirCapSeq-VERT) was used to search for viral sequences within the malignant T-cells in Sézary patients. Two retroviruses, HERV-K and HTLV-q, were found in all patient samples. However the fact that these could have been false positives suggested that more work needs to be done. Future studies are needed to determine whether these sequences play a role in causing disease or are false positives. Small sample size and only SS patient samples were tested, which limit any confirmation that these viruses pay a role. Further investigation is necessary to determine whether these may represent an important factor in cutaneous lymphoma disease development.

Therapeutic options for advanced cutaneous lymphoma are limited and the identification of novel markers may allow for the development of targeted therapies. A study into the immune markers TIGIT and Helios that are highly expressed in Sézary Syndrome were investigated as to their role in immune suppression. The study found that these two markers were found more often in SS than in MF patient samples and provide insight into the immunosuppressive nature of SS. The data suggest another potential means of finding a target for future therapy development.

A study reviewing targets for early diagnosis of SS in the blood evaluated the cellular characteristics in patients with suspected SS. The study showed that the panel of seven biomarkers (PROM1, GOS2, CMTM2, C2orf40, PAM, GNMT and NEXN) can be helpful in early diagnosis of SS which may translate into more informed treatment decisions.

A study reviewing additional markers for early diagnosis looked at IL-13 receptors expressed by the CD4+ T-cells in SS. IL-13 activates growth of Sézary cells in the lab. It was concluded that IL-13 and its signaling agents are novel markers for cutaneous lymphoma malignancies and could be potential therapeutic targets for intervention.

KIR3DL2 is a recently discovered marker of the malignant clonal cell population in SS. A study was conducted to evaluate this as a diagnostic, prognostic and follow-up marker for SS. KIR3DL2 represents a diagnostic target as well as a target for disease progression management and could be an early marker for relapse or progression. Promising pre-clinical results were obtained using an anti-KIR3DL2 antibody able to promote cell death, leading to depletion of the cancerous cells. This approach could be promising as minimal side effects are expected from the antibody mode of action. Clinical trials are on the horizon.
Targeted therapies show great potential in treating cancers and hope to help advance understanding and treatment of cutaneous lymphoma. A study of the cell adhesion molecule 1 (CADM1) in the leukemic cells and skin infiltrates of Sézary patients was conducted. The research showed that CADM1 is a diagnostic cellular marker for progressive/resistant SS. More research into this area is required to understand how this can be used as a therapy target.

**Primary Cutaneous B-Cell**

Primary cutaneous B-cell lymphomas are rare lymphomas with an estimated annual incidence of 2-2.5 per 1,000,000 people. They are classified into three types: marginal zone lymphoma (MZL), follicle center B-cell (FCC) or diffuse large B-cell lymphoma (DLBCL) and diffuse large B-cell lymphoma, leg type (DLBCL-LT). The management and prognosis varies between these subtypes. Studies conclude that there is good prognosis for both MZL and FCC following first line skin directed therapy. While systemic spread of these variants is rare, relapses are frequent. DLBCL has a poorer prognosis and required first line systemic therapy.

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (pcDLBCL, LT) is a rare and aggressive form that shares genetic and phenotype characteristics with diffuse large B-cell of activated B-cell subtype. The study concluded that despite the similarities of the two types of lymphoma, the lack of B-cell receptor signaling in pcDLBCL, LT points to a different role of this receptor which may have implications on the behavior and treatment targets for this aggressive form of cutaneous B-cell lymphoma. Studies into the role of PD-L1 expression plays in all forms of primary cutaneous diffuse large cell lymphoma, including leg type, may provide a promising therapeutic approach to treating this group of rare cutaneous lymphomas. High prevalence of MYD88 mutations in pcLBCL-LT as a diagnostic marker may also be valuable in determining treatments and prognosis.

**CD30+ Lymphoproliferative Disorders**

Studies reviewing the connection between atopic disorders (dermatitis, hay fever/allergic rhinitis, asthma, etc.) in patients with primary cutaneous CD30+ lymphoproliferative disease found:

- Lymphoproliferative patients had a lower lifetime prevalence of allergic rhinitis/hay fever for lymphoproliferative-A but not the case for lymphoproliferative-C. Lymphoproliferative-C patients had a higher incidence of history with eczema than other types of lymphoproliferative patients. Patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) had a decreased prevalence of allergic rhinitis/hay fever. Risk of penicillin allergy for patients with pcALCL was higher.
- The findings of CD30+ cells co-producing IL-13 and Th17 cytokines provides new evidence linking CD30+ lymphoproliferative disorders to atopic disorders.
Mutations, Epigenetic and Genomic Landscape of T-Cell Lymphoma

The deep cellular landscape of diseases and cancer continues to show that the differences between all diseases is becoming more defined and focused. As we learn more about the set of DNA within a single cell (genomic profiles) of these complex diseases, it becomes more of a challenge to determine what component plays a critical role and those that do not. However, complexity can be of use in how these genomics impact the various cell pathways and what isn’t working properly. It’s important to look through the lens of pathways rather than genes and look for therapeutics that target the pathways. For example, the genomic profiling of Sézary Syndrome, as diverse as it can be, can help to uncover patterns of mutations, specific effects of those mutations of the genes, and what pathways are activated - thus to begin to recognize the drivers of the disease. Signaling pathways play a critical role in highlighting new opportunities for therapy targets. We are starting to see some genes emerge as potential epigenetic targets.

Since 1997, multiple studies have shown defective signaling pathways that regulate cell death and other ways cells evade detection. Targeting ways to promote proper cell death by manipulating pathways was the focus of the study presented. It appears that defective signaling pathways in cutaneous lymphoma and chronic dermatitis are similar, which point to why some cases of atopic dermatitis may evolve into cutaneous lymphomas. These pathways also provide novel, cost-effective therapeutic options for patients targeted to a specific clinical situation.

A study investigating cell death and the effectiveness of using chemotherapy and other therapies for cutaneous lymphoma researched the specific pathways that cells use to protect themselves from these therapeutics. Basically, some of the chemo agents activate these pathways which inhibit cell death and therefore are not as effective as a therapy in treating cutaneous lymphoma. This is important to understand as it appears that chemotherapeutic agents induce “protective” signaling in cutaneous lymphoma which enhances cell survival. There are places in the skin where cell death never takes place and this is where the malignant cells can hide.

The mutational landscape of cutaneous lymphoma is complex. The genetic mutation environment is very diverse, making it a challenge to find the critical markers and targets that create disease and support progression. The only exception to this is TP53 inactivation in cutaneous lymphoma. Besides the deletions that affect over 50% of SS patients, it has also been found that there are recurring mutations in TP53. After TP53, the next thing identified is somatic mutations in epigenetic regulators representing a recurrent event in cutaneous lymphoma, multiple signaling pathways that are activated by mutations. Increased activation of the NF-κB, JAK-STAT and MAPK pathways are frequent in cutaneous lymphoma. However, more needs to be investigated to refine and focus on the components that are of most critical value in diagnosing and treating this complex group of diseases.

A study into the critical importance of the JAK/STAT pathways in cutaneous lymphoma was conducted that strengthens the hypothesis that this signaling pathway is dysfunctional in cutaneous lymphoma. Future work will screen gain-of-function mutants against libraries of small molecular inhibitors with the aim of identifying novel therapeutic targets for modifying what is going wrong in this pathway.
Development of an in vitro platform for screening targeted molecular agents which would help to move advances in genetics into a useful clinical practice for diagnosis, prognosis and treatment selection. Many studies published in the last few years have shown a complex landscape, making it challenging to bring this new science into the clinic. The goal is to find optimal combinations of targeted therapeutic agents for each patient by using this new platform to test the combination in the lab first rather than in the patient. This process may help to understand how these agents will work together and which combinations would be most beneficial.

Lessons were learned from novel mouse models in the lab using next generation sequencing. Generation of this animal model of cutaneous lymphoma demonstrates the causative roles of dysregulated STATE3 signaling in the path of disease and establishes a pre-clinical model for evaluation of novel therapeutic strategies for treating patients. Perhaps we will also learn that micro infections play a role in disease progression. There is still much work to do and much to understand about a possible role of bacterial and environmental antigens in cutaneous lymphoma and what are the mechanisms for triggering disease or progression.

Using high throughput T-cell receptor sequencing to better diagnose and treat patients with cutaneous lymphoma. Differentiating between cutaneous lymphoma and other inflammatory diseases is still very difficult. Most patients report that it takes more than five years to get a confirmed diagnosis. Using this new high-powered tool can enhance diagnosis, identifying which treatment regimens actually kill the malignant T-cells and potentially identify patients at high risk for disease progression. An exciting new method that can translate into earlier diagnosis as well as understanding the effects of treatment.

CLINICAL TRIALS & STUDIES

Multinational Studies

Cutaneous Lymphoma International Consortium (CLIC): CLIC is an international collaborative approach to science bringing together clinics from around the world. This network is not only global in nature, but also interdisciplinary, incorporating all clinical specialties. Projects include creation of an international federated biobank that harmonizes what specimens to collect, how to collect them and how to store them. When a project of discovery is presented, everyone in the Consortium will have the sample at their site so all the research can be easily analyzed and compared. 55+ centers are collaborating as part of this worldwide alliance. It is a large-scale initiative enabling research to be conducted in a way that will help move the understanding of cutaneous lymphoma forward faster and with more precision.

CLIC - International Prognostic Index Study
The CLIC embarked on a retrospective study for advanced MF and SS to inform the development of an international prognostic index. The intention is to develop a prognostic index by collecting data at diagnosis and measuring it against survival. This index is useful because of the range of survival among patients. To impact long-term survival and quality of life, poor prognostic factors need to be identified with an attempt to treat proactively. A prognostic index
was begun in 1999, but 4 prognostic factors have been now identified based upon this large retrospective study of 874 patients with complete data sets. The study looked at patients with all stages of disease: low risk group with 5-year survival versus high risk group with worse survival rate. The next prospective study will collect well defined parameters at first diagnosis, stage progression and annual follow-up for both MF and SS along with variables that will be tested against overall and progression-free survival. The study will recruit a minimum of 1000 patients with early-stage disease and 500 with later-stage disease. The study opened in Europe in early 2017 and is recruiting participants. 46 centers are participating and currently have 432 patients enrolled from 34 centers from 14 countries across 3 continents. Early data shows:

- 77% with early stage (331 participants) 50% IA, 10% IB;
- Smaller group of IIA of 137 participants;
- 86% classical MF;
- 22 patients (14%) FMF;
- Later stage data included 101 patients broken down into:
  - IIB 36%
  - 15 IIIA
  - 8 IIIB
  - 2 IVA
  - IVA2 11 patients
  - Stage IVB patients also included
- Significant difference in age between IA and IB
- Early stage (57 average age) versus late stage (67 average age)
- Data shows that patients with advanced disease are not being diagnosed later than early stage but have a different and more aggressive variant of the disease;
- CD4:CD8 ratio significantly higher in IB than IA;
- Blood parameters are not clear yet, but noticing some patients fall between B1 and B2. Data needs time to mature;
- 39% early stage patients had lymph node imaging;
- 10% of those with imaging had lymph node of 15mm or greater in one axis.

The goal is to give patients better information in the future about what treatments are working and how long will it take to see the impact, etc. It will be useful in clinical practice as you can see the patients’ history of treatments. There is more information to gather about how many treatments a patient has had, time to response and other details that will be helpful in informing treatment decisions and potential therapeutic interventions.

**CLIC - Global Pattern Study**
The second CLIC study will look the relationship between treatment approaches and survival. So far, the information collected includes:
• 853 patients IIB or higher diagnosed from January 2007 with treatment information.
• Similar number of patients from Europe and US, with Japan, Australia and South America contributing.
• Median age 64. Most frequent stage is IIB, followed by IVA and prevalence of stage III in non-US centers;
• Median number of treatments per patient was two;
• Most a patient has tried was 24 treatments and there is a wide range of the number of treatments;
• Very high number of treatment approaches with 38.9% patients receiving four or more treatments;
• High unmet clinical need for treatments in these patients;
• Most frequently used treatments refer to immune modulators like photopheresis, bexaratone, interferon, and multiple combination treatments;
• Look at distribution of US and non-US centers. Several differences in treatment approaches. Bexaratone and photopheresis used more frequently in US.
• HDAC inhibitors not approved in non-US;
• Reasons are due to differences in regulatory approval. Access to new drugs through clinical trials which may have variable geographical regions;
• Geography did not have any impact on survival;
• Chemotherapy as first treatment is associated to a higher risk of death and thus other therapeutic options should be preferable as first treatment approach.

International Pathology Pilot Study investigated the validation of central pathology review in advanced stage cutaneous lymphoma. This was a pilot project with the idea of studying a cohort to evaluate the feasibility and reproducibility in a small scale setting using a retrospective approach with two panels of dermatopathologists. Plan to enroll 500 patients going forward. Scan the slides into a system so they can be disseminated through a server for review. 76 cases from 11 centers reviewed by 3 independent dermatopathologists.

Conclusion of the pilot study review showed digital slide scanning is feasible and a useful tool. Central pathology review is mainstay for adequate, accurate and reproducible way of the analysis of prognostic biomarkers in advanced stage disease.

US Cutaneous Lymphoma Coalition Clinical Registry: Registry group was founded in 2007 to develop a long-term clinical registry used by individual treatment centers and groups that could work together and integrate patient data from the different institutions. The platform allows for exchange and/or capture data from other platforms with translation efforts. Goal is to help inform patient care and looking for factors that can influence treatments. In the United States looking at incidence and geography. Open to all centers with at least 3 patients.
EPIDEMIOLOGY & POPULATION STUDIES

Trends in cutaneous lymphoma:

• MF was noted to be increasing in incidence 26 years ago in United States. Multiple reports have since documented further increases, the cause of these increases are controversial.
• Variety of challenges including terminology, complicated research and dependence on disease definitions used in the clinical community.
• Cutaneous lymphoma subtypes have changed in classification further complicating analyses.
• Definitions must extend to the broader diagnosing community.
• Using the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the US, (SEER covers about 25% of population) showed that around the year 2000 the increase in incidence of cutaneous lymphoma had stopped and now fairly level as shown in the SEER database through 2009.
• 1998 estimated year that the increases in incidence in cutaneous lymphoma in the US began to level off.
• Up to that point, beginning in 1973 the incidence was increasing at 6% per year.
• Male to female ratio decreasing although still male predominate disease.
• Geographic differences appear. For example San Jose and SFO have very different rates.
• Cannot reliable look at MF vs. non-MF
• Dramatic flip in diagnosis and recording to more cutaneous lymphoma not specific.
• Subtype data is not good enough to distinguish this information into trends. Need more data to be more reliable.
• Similar trend in incidence in cutaneous B-cell lymphoma. Has leveled off as well (as of 2010). Incidence seems to have leveled off to about 10 per million per year. Cutaneous lymphoma about 4 per million per year. Mortality is substantially underestimated and many questions remain.

Possibilities for prevention:
• Primary prevention distinct from detection and treatment.
• Geographic comparisons of cancer type can produce clues to environmental and occupational risk factors.
• There’s very little literature currently for non-Hodgkin lymphoma and even less within that for cutaneous lymphoma.
• World trade center survivor registry is an exposure registry which has shown an increase in non-Hodgkin lymphoma in the survivors.
• Problem is the studies include all types of lymphoma.
• Occupational risks for some categories; including peripheral T-cell lymphoma (PTCL) from Interlymph Consortium.
• Small number of studies and exposures associated with MF. Most the same as other non-Hodgkin lymphomas and one that includes the cause of Lyme disease curiously.
• Unlikely that all types of non-Hodgkin lymphoma are involved and need to look at the exposure information specific for cutaneous lymphoma.

Individual Country Reports:

Asia:
• Relative frequency and outcome in cutaneous in Korea for a 10 year period was 395 patients diagnosed with primary cutaneous lymphoma.
• Few reports from Korea, Japan and Singapore.
• Measure changes in cutaneous lymphoma frequency trends through comparison of subgroups of patients between 1994 and 2013.
• Highest incidence of MF. Most common physical presentation was patches. Only half presented with multiple skin lesions. Similar prognosis to other regions.
• NK/T-cell higher rate in Asian population.
• Frequency of MF 29.4% less than in US and Europe.
• Present data revealed an increasing frequency of cutaneous B-cell lineage over time.
• NK/T-Cell lymphoma has the poorest survival outcomes.

Latin America:
• CTCL 90%, CBCL 5% in Latin America.
• CTCL is 90% in San Palo, Brazil versus two other regions that are a little less.
• Similar prognosis survival curves to others reported.
• In general, reduced proportion of cutaneous lymphoma when compared to the US and Europe.
• Northeast of Brazil is endemic for HTLV-1 and increased number of all is observed.
• More studies are needed to better characterize genetic and environmental factors associated with different cutaneous lymphomas in Latin America.

Middle East:
• Cutaneous lymphoma is the second most common extra nodal non-Hodgkin lymphoma in Saudi Arabia.
• Single study in Riyadh: 43 patients, 58% classic, 41% hypopigmented.
• Retrospective study from 2010-2016 included 125 patients from 5 years to 85 years old. All different presentations. Gender showed 58% male, female 42%. Most common age was between 30-40 representing 20 people, followed by 40-50 age group. Notice that younger population (under 20) is around 12 people. Pattern of presentation are typical plaques and patch but hypopigmented was third most prevalent followed by polkioloderma presentation.
• Not a lot of Sézary Syndrome.
• Four patients with rheumatoid arthritis all females. Question as to whether there could be a correlation between the two. Patients had other cancers (Hodgkin, thyroid, rectal and breast). Below age of 10 were all boys; 2/3 between age 10-20 were male.

In the Laboratory - Translational and Pre-Clinical Studies

While there have been ongoing efforts in recent years to understand cutaneous lymphoma and search for new treatments potentially with a curative outcome, much work is still needed to fully comprehend the complexity of this disease. As that research continues, additional work is being conducted to find new therapeutic approaches with higher effectiveness with milder side effects. There was much excitement around the preclinical data that was presented. Highlights of this scientific research follows:

• **NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)** is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. Incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. (Wikipedia definition). Targeted therapy in this specific pathway would leave non-malignant T-cells unaffected by the treatment and restore the cell death mechanism in the cutaneous lymphoma malignant cells. Dimethylfumarate (DMF) was studied in the laboratory environment that showed effectiveness in inducing cell death. The promising preclinical results indicate that these results may translate into successful clinical treatment with this drug. Additional study is required to confirm these first observations.

• **A microRNA** (abbreviated miRNA) is a small non-coding RNA molecule that regulates expressions of hundreds of genes impacting cellular processes. Specifically, miR-155-5p appears to have a strong link to cutaneous lymphoma. Research conducted into treating with MRG-106, which is a drug that inhibits miR-155, support the theory that this targeted therapy could be a new treatment in cutaneous lymphoma. A first-in-human clinical trials (Phase I) study has been initiated with the goal of studying the safety and tolerability of MRG-106.

• Phase 1 study reviewing the potential of a different kind of photosensitizing agent (silicon phthalocyanine 4 “Pc4) that can be used by patients who are at high risk of cardiovascular disease. This small study evaluated the safety and toxicity of this agent in 11 subjects. The results showed that Pc4 may be an alternative photosensitizing agent to use with photodynamic therapy for people with higher cardiovascular risk (history of smoking, hypertension, diabetes, hyperlipidemia, etc).

• **CD70 (“Cluster of Differentiation”)** is a protein expressed on highly activated lymphocytes (like in T- and B-cell lymphomas - Wikipedia definition). It is therefore suggested that anti-CD70 antibodies might be a possible treatment for CD70 positive lymphomas as normal lymphocytes have low CD70 expression. A preclinical investigation of a potential drug-antibody conjugate, SGN-CD70A, is being clinically investigated for use in treating B-cell lymphoma. A preclinical study to determine if this would also be a good target in T-cell lymphoma was undertaken that concluded that CD70 is expressed in both nodal and cutaneous
T-cell lymphomas, suggesting that this drug, SGN-CD70A could be a promising anti-tumor agent for treating cutaneous lymphomas. Additional research is required to explore this targeted treatment option.

- Synergistic effects of combining romidepsin and mechlorethamine were studied in the laboratory environment to determine their interaction and potential together. The study concluded that there is a harmonious relationship between these two drugs that make a strong argument for testing this specific drug combination in clinical trials, particularly for patients with Sézary Syndrome.

- Retinoic acid receptor alpha (RAR-alpha) and retinoid X receptor (RXR) form RARα/RXR and are a novel pathway for Vitamin A signaling. A study investigating the combination of bexarotene with an agent that targets the RAR-a/RXR pathway showed that reducing the concentration of bexarotene in conjunction with augmentation of a RARa agonist, could minimize the adverse side effects of bexarotene while still having the desired therapeutic result. The study underscored the need to investigate in more detail the way vitamin A works in treating cutaneous lymphoma.

- Laboratory study investigated the combination of a novel histone deacetylase inhibitor (HDACi), butyroyloxymethyl diethylphosphate (AN-7) with a known treatment used for advanced cutaneous lymphoma, doxorubicin, proved that this combination could be a therapeutic modality in treating advanced disease.

- Using resminostat, an orally available HDACi is already in phase III clinical development. 300 non-cutaneous lymphoma patients have been treated with this drug that showed adverse effects were mild to moderate, manageable and reversible. A study to review the potential therapeutic use for advanced stage cutaneous lymphoma patients as a maintenance treatment showed promising results in the laboratory cell lines. A clinical phase III trial to evaluate this is in patients in preparation.

- A clinical laboratory investigation into the use of an available immunomodulatory agent, lenalidomide that shows clinical effectiveness in other forms of leukemia and non-Hodgkin lymphomas was studied for use as an agent in cutaneous lymphoma. The study observed that this drug enhanced cell death and that lower concentrations of the drug were more effective. More studies are required to confirm this, but the data is encouraging for integrating this drug into the treatment portfolio for cutaneous lymphoma as a single agent or potentially in combination with other drugs.

- c-Myc is a regulator gene that plays a role in cell cycle progression, cell death and cell transformation. This gene is mutated in many cancers and has been studied frequently as a potential therapeutic target. There have been some new drugs developed to target this gene, but to date, none have been effective. A study was undertaken to review the drugs that target this that are already in use in the clinic to see if there was an impact by combining them in different ways to treat cutaneous lymphoma. The results show strongly that TGR-1202 (a first-in-class dual PI3Kdelta/CK1 epsilon inhibitor) demonstrated promising clinical activity with an excellent safety profile in phase I/III clinical trials in lymphoma and may be an excellent tool for therapeutic targeting of the c-Myc gene in cutaneous lymphoma. There is now a phase I clinical trial underway for TGR-1202.
THERAPIES & CLINICAL TRIALS

There has been much activity in new therapy development and clinical trials to collect data on the effectiveness of these new treatments. Research into how cutaneous lymphomas functions has been a major focus so that good targeted drugs can be developed or studied for use in the different subtypes. There is not yet a good sense of which treatments will have a positive impact on an individual patient’s disease. However, many good biopsy specimens are being gathered and will help inform future studies on the impact of the different drugs. Combination therapy clinical trials along with many new, novel agents currently in pre-clinical study and early clinical development show promise. The challenge is to choose the best therapies to move forward with which requires collaboration of all institutions globally to capture as much information as possible to help inform treatment decisions.

Highlights of new treatments in clinical study:

• KIR3DL2, a member of the killer immunoglobulin-like receptor (KIR) family appears in malignant cells in Sézary Syndrome and transformed mycosis fungoides (TMF). KIR3DL2 may also be of prognostic value and therapeutic value. First in human, open label, multi-center phase I study of a new drug targeting KIR3DL2. This phase 1 study using the compound, IPH4102-101, will be fully completed in 2017 and followed by an expanded phase II study with the primary objective of assessing safety and tolerability of increasing IV doses of this drug as a single agent. Preliminary data shows it is well tolerated in the elderly and in heavily pretreated patients. The study is continuing to enroll.

• E7777 is the reformulated version of denlieukin diftitox (brand name was Ontak) which was previously approved by the FDA in the US. A multi-center, open-label, single-arm study was conducted to select the proper dose for the main study in which efficacy and safety will be assessed. The main study is now open in six US centers and one in Australia with planned enrollment of 70 patients. This compound targets CD25 which is seen more in MF patients than in Sézary Syndrome.

• While there are multiple treatments available for MF, most still result in relapse of disease. New treatment strategies that combine synergistic treatments together that result in longer duration of remission and improved response rates are needed. Moving to low-dose total skin electron beam (TSEB) in combination with other compounds that boost the immune system, using specifically recombinant human interleukin-12 (NM-IL-12) which has been shown to be effective immune booster. One of the main functions of low dose TSEB is to generate interferon. It is speculated that IL-12 is suppressed and this results in tumor cell evasion and escape. Early results of combining NM-IL-12 with low dose TSEB demonstrate that these two modalities can be safely administered together in a small group of patients showed encouraging results. This study is continuing to enroll. Additional information can be found on ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02542124.
• Interim analysis of a Phase II clinical trial using topical pimecrolimus in early stage MF has shown activity with a good safety profile. This treatment is an immunomodulating agent used in the treatment of atopic dermatitis. It is available as a topical cream under the trade name Elidel. Ongoing studies will investigate the immunohistochemistry and mechanisms of action in treating early stage MF.

• Early Phase I study of an anti-CD37 antibody which appears to have an impact on cell death within the cell signaling pathway. It is the same technology used in brentuximab vedotin, but directed against CD37 proteins rather than CD30. Data from this early stage study showed that AG567E (the current name of the compound) has a favorable safety profile and has demonstrated signs of activity in cutaneous lymphoma. Clinical trial information can be found on ClinicalTrials.gov: https://clinicaltrials.gov/show/NCT02175433

• Malignant cells in cutaneous lymphoma express PD-1 on their cells which inhibits cell death. This study explored the clinical activity of pembrolizumab (Keytruda brand name), which is an immune checkpoint inhibitor of this cell death pathway. The study showed that this compound has significant clinical activity with durable responses in previously treated cutaneous lymphoma patients. A Phase II trial combining pembrolizumab with interferon-gamma is being developed based upon these results. The study is not yet open. Additional details can be found on ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT03063632?term=pembrolizumab+combined+with+interferon+gamma+and+cutaneous+lymphoma&rank=1

• A retrospective review of incorporating leucovorin with treatment of cutaneous lymphoma with Pralatrexate (Folotyn brand name) found that this additional helped to alleviate a known side effect of mucositis in 77% of patients. Mucositis is a challenging side effect that can impact the ability of the patient to stay on the treatment even when the treatment is effective. Incorporating leucovorin into the treatment regimen has a positive effect of reducing the challenges of this side effect.

• The standard 30Gy dose schedule of total skin electron beam (TSEB) has been very effective with high response rates. However, there is interest in lowering the standard dose to reduce toxicity and test level of response in patients in the United Kingdom. Low dose TSEB (13Gy) was introduced in 2011 with 103 patients completing the lower dose treatment. The overall response rate among these patients was 87%. The results had similar high overall response rates to higher dose TSEB while lowering the toxicity of the treatment resulting in better patient experience and allowing for future treatments with TSEB.

• The experience with mechlorethamine gel (Valchor trade name) in France in a retrospective study of 107 cases across France where patients were treated with this topical gel. The study showed that most patients had used prior treatments, mostly topical steroids and were treated for an average of 162 days. 80% of patients were using this in conjunction with alternating with strong steroids. Similar to the American study, the predominate adverse effect was topical dermatitis. Overall the study showed that this topical treatment is well tolerated and shows
effectiveness for early stage MF. This treatment was recently granted marketing authorization by the European Commission for mechlorethamine gel (trade name Ledaga) for the treatment of mycosis fungoides.

**Stem Cell Transplant**

The role of stem cell transplantation in cutaneous lymphoma is challenging to study because of the uniqueness of each patient’s disease, lack of uniformity of conditioning regimes between the different centers and the small numbers of patients to study. The review of retrospective data shows the long term outcomes are similar. At 200 weeks, progression free survival is estimated at 60% with large registry data showing a survival curve around 40% at five years. This is an improvement in survival of patients with advanced disease and certainly an option worth considering. From the data, Sézary Syndrome patients seem to do better after an allogeneic transplant. It appears that a reduced conditioning regime has an impact with no difference in overall survival comparing the reduced conditioning regime versus the full conditioning. However, stem cell transplantation always comes with the risk of complications from the transplant, post-transplant infections, relapse of disease, etc. Transplants are being offered to older and older patients, but optimal timing for each patient is individual. Important considerations in making a decision to move to transplant should take into account age, donor selection and availability, optimal conditioning regimen and overall health.

An update on stem cell transplant from Italy showed an extension in age up to 70 for advanced MF/SS that had available donors. The total number of transplant patients in Italy is now 36. Their experience also concludes with the high risk of this modality for patients although if the transplant is successful could be a potential cure. The open issues are still which patients are best suited for transplant, what is the timing and what should the conditioning regime be to support best possible outcomes.

**Clinical management & Quality of Life**

The ongoing challenge is determining when to treat patients, especially very early stage and what to treat with. One perspective is to treat for alleviation of symptoms. In this area patient-reported outcomes are critical to learn more about how effectively we are treating the disease. Is there risk of infection, risk of malignancy and progression? Or is the major goal reducing disease burden resulting in better quality of life and preventing progression? There are few principles around treating localized disease versus treating widespread disease. Should all skin be treated or is systemic therapy a better option? The goal is to avoid immunosuppression, minimize toxicities that are cumulative and a long-term treatment timeline. TSEB for example, has had a major evolution of dosing but is one of the more de-humanizing treatments. Challenge is how to choose the appropriate therapy that has the maximum effectiveness, reduces disease burden and improves quality of life of an individual. We are now starting to learn how to use these therapies in a more humane way, taking into consideration the whole patient and their personal journey with this disease. Reviewing how to treat sanctuary areas with phototherapy and how best to deal
with disease in these areas. Reviewing why patients need targeted therapy to minimize further compromise of adaptive immunity and how to use treatments to get at those malignant T-cells that are overwhelming the good T-cells that are trying to keep the immune system healthy. These are some of the questions the clinical community is beginning to ask now that there has been more experience with current treatments, data is being collected and reviewed and new treatments are being developed based upon new understandings about this disease and its way of behaving.

There have been concerns about the additional carcinogenic affect of phototherapy on patients. Most of the data has been reported in psoriasis. The analysis was to determine if UV exposure in MF patients lead to mutations that propel progression or enhancement of cutaneous lymphoma. There has been some evidence to suggest there is some role of radiation from phototherapy on disease. A retrospective analysis was performed reviewing cases form 1979-2016. The analysis revealed that patients who received phototherapy took longer to progress, survived longer. No one died of melanoma or other skin cancers in patients that had developed them. The conclusion is that the therapeutic effects of phototherapy appear to outweigh any of its potential adverse effects on disease progression or development of other skin cancers.

Challenges in treating sensitive areas of the body. The eyelids, for example, are a sanctuary area that are typically difficult to treat. How to manage the patient’s disease over the long term when the disease persists in these hard to treat areas. These can be quite symptomatic and can be visible, such as on the face. Topical treatments are limited in sensitive areas such as the eye area. Some information in the literature about modifying treatment to use therapy such as excimer laser or low dose radiation therapy, which may also have a systemic effect. In a single center study reviewing cases between 2011-2016 of MF patients, it showed that eye lid involvement is common and can be seen even in early disease. While selected skin directed therapies can be used judiciously, patients may require systemic agents to treat disease in difficult to treat sanctuary areas to manage the disease optimally.