

EORTC CUTANEOUS LYMPHOMA GROUP
Scientific Meeting: Cutaneous Lymphoma - Translating Science into Patient Care

Presentation Highlights

Susan Thornton, CEO of the Cutaneous Lymphoma Foundation, attended virtually the EORTC-CLG Scientific Meeting held in October 2021. The following are Susan's notes from the clinical presentations, highlighting points of particular interest to the patient community

Why does early diagnosis and intervention in mycosis fungoides (MF) matter - a discussion:

It is critical to provide patients with appropriate care, disease management and a long-term care plan.

- What are challenges to early diagnosis?
 - Lack of clinical familiarity with the disease. Mycosis fungoides (MF) is often missed because the dermatologist has a low suspicion of cutaneous lymphoma. Awareness in the field is critical - you cannot see something if you are unaware of its existence.
 - Misdiagnosis - unless the clinician thinks of cutaneous lymphoma, it may be mistaken for inflammatory disease. MF can often hide behind more prevalent inflammatory diseases. It is important to monitor the patient's patches over time in order to treat appropriately.
 - Difficult to see, subtle patches in early stage MF are often missed.
- Early intervention considerations
 - "Watchful waiting" is outlined as an option in the international guidelines but most physicians and patients prefer early intervention if appropriate.
 - MF can mimic atopic dermatitis both clinically and histopathologically; cyclosporine and other immunosuppressive agents should be avoided unless MF is ruled out.
- Recommendations
 - Because early stage disease is challenging to diagnose, education is critical for general dermatologists and other healthcare professionals. Education can raise their awareness to monitor those patients who are suspicious for a diagnosis of early stage MF.
 - Clues that general dermatologists can look for are persistent rashes that are resistant to treatment.
 - Even when a definitive diagnosis is not able to be made from biopsies or a clinical review of the presentations on the skin, if there is a suspicion of MF, close clinical follow-up over a few years is critical.
 - Early stage folliculotropic MF (FMF) should be included in the diagnosis process. Early stage FMF tends to involve exposed skin and less often the less exposed, sun-protected part as in classic MF.

The use of technology and new tools in clinical practice

The current diagnostic method for cutaneous lymphomas may create delays in diagnosis. New technologies in support of better diagnostic tools for early determinations of cutaneous lymphoma are showing promise.

- Flow cytometry and machine learning in diagnosing Sezary syndrome
 - Using flow cytometry and machine learning to delineate tumor-defining cells in Sezary syndrome (SS) can allow for discrimination between SS and benign erythroderma (redness all over the body);
 - Machine learning can be used as a method to find patterns. Inputting large amounts of data into a database enabled the identification of the cell population correlated to CD4+ T-cells in SS patients. The data was validated in an independent cohort, creating the first successful machine learning morphology-based diagnosis for SS;
 - Using current diagnostic methods of flow cytometry plus this kind of artificial intelligence in data analysis equals a powerful tool to contribute to data-driven diagnosis and studies of disease progression for the future.
- Potential of Artificial Intelligence (AI) in the diagnostic process
 - Currently the assessment of skin for MF typically incorporates two analysis tools, the mSWAT (link to mSWAT article) and BSA (body surface area). The mSWAT is more representative and used in research and clinical trials but is time consuming and challenging to implement into daily practice.
 - AI is used today for melanoma and non-melanoma skin cancer, and may represent a future approach for MF.
 - AI uses the computer to mark lesions, extracting information to create small patterns. This process is repeated multiple times. Based on this data, the technology creates models that may be helpful to assess skin in MF/CTCL to support the diagnostic process.
- Advances in mobile app technology, may also help to capture the patient's lesions outside of the clinic to be used as an early diagnostic tool in the future. Work is also being done to create methods to capture full body scans that calculate the body surface involved.

Clinical Discussion on Therapies

- Extracorporeal photopheresis (ECP)
 - A review of immune modulators currently used as therapies, shows that extracorporeal photopheresis (ECP) and interferon seem to provide one of the better approaches to creating a good duration of response, even if not total response, with lowest toxicity to support best quality of life.
 - The role of ECP in the management of CTCL was shared by the Australian clinicians. Their single center study looked at using ECP early in treatment for patients with erythrodermic MF and SS. The data points to potential prolonged survival outcomes. Additionally ECP had a longer time to next therapy (14 months) as a monotherapy, especially compared to other monotherapies used for treatment.
- Mogamulizumab associated rash (MAR) - With the increased availability of mogamulizumab, more research is being done related to MAR. Current findings include:

- The nature of MAR remains unclear although it appears to have a distinct pattern that can mimic CTCL. It was also found that MAR is likely (versus disease progression) where cell samples showed a lack of clonality.
- The efficacy of mogamulizumab may be underestimated because MAR is misidentified as relapsed disease without thorough investigation. Premature discontinuation of its use may occur.
- A study related to MAR from a center in France showed that the patients who got the rash had a slightly lower number of pre-treatments, suggesting the need of a baseline with patients who may develop the MAR having a different status than those who do not. They also found that few patients experienced a second MAR after the first. Additionally, patients who had a rash appeared to have a higher overall survival and also had a very specific gene expression pattern.
- There is still much to learn about this therapy based upon the experience of patients in clinical practice to determine how to differentiate those who may respond with a MAR and those who do not.
- It is also important for clinicians to be aware of how to treat through this challenge as MAR may need more of an immune reaction strategy versus a drug reaction one. More discussion and consensus based on experience data is required to determine an appropriate clinical strategy for treating this issue.

Quality of Life - Update from PROCLIFI* and other institutional studies

It is important for clinicians to be aware of the emerging themes found in the quality of life (QoL) data. The studies revealed that over time, patients' quality of life tends to go down. It is important in clinical practice to monitor individual patients as a reflection of their personal QoL ratings - a high rating for one person might be a low for someone else. It is important to qualify the patient experience beyond just the number to better understand what is behind the rating number for that patient.

Findings from the studies include:

- QoL gets worse with stage progression. For example, IIB tumor patients have significantly impaired QoL.
- Patients report the following concerns that clinicians should be aware of:
 - Annoyance or frustration with the disease and/or treatments
 - Worry about their condition might be serious or getting worse; or that the condition of their skin may worsen
 - Emotional worry about incurability and side effects
 - Worry about side effects from skin medications/treatments
 - Physical changes in appearance can have a significant emotional impact. For example, alopecia provokes emotions of anger, frustration and embarrassment
 - Itching, sensitivity and irritation
 - Female patients reporting itch symptoms and hypopigmentation more often than men
 - Itch can be expressed in different ways - skin hurting/sensitivity, redness, scaling

- Sleep issues when there is a higher burden of disease, skin ulceration and itch
 - Functional concerns related to clothing and feeling tired
 - Younger patients worried more about the disease getting worse and were also concerned about alopecia
- The role of illness perception and a patient's personal beliefs about their disease impacts quality of life
- Disparities that impact on QoL
 - Age - 40-59 age group report the highest impact on their life and a higher emotional impact
 - Stage - there was a trend toward a higher impact on QoL for late stage and more emotional impact on early stage
 - Race/ethnicity - There is an overall significant QoL difference based on race/ethnicity; additionally, black or hispanic patients reported a lower understanding of the disease
 - Social determinants of health may have impact on disparities

In summary, more work is needed to discover what data is still missing from the studies, and to better understand the long-term impact of these QoL issues and how they may change over time and/or with treatment. New approaches to measuring and qualifying the underlying issues that may be causing the QoL scores may help create pathways for supporting patients who are experiencing these challenges through referrals for other types of care or support beyond the treatments. There are current limitations in data collected from individual institutions that may not be generalized. Additional studies need to include a larger number of patients, inclusion of a broad range of demographic groups and ages.

*The PROspective Cutaneous Lymphoma International Prognostic Index (PROCLIPi) study was launched in 2015 with the long-term goal of developing a prognostic index for cutaneous lymphoma. In addition to the clinicopathological and genotypic data, treatment responses and quality of life are being collected, alongside a federated tissue biobank for translational studies.

COVID Related Research - International Cutaneous Lymphoma Pandemic Section

In response to the COVID-19 pandemic, the US Cutaneous Lymphoma Consortium and EORTC-CL Task Force developed emergency guidelines for patient treatment. The International Society for Cutaneous Lymphoma (ISCL) created the International Cutaneous Lymphoma Pandemic Section (ICLYPS) to analyze CTCL outcomes during the COVID-19 pandemic.

The ICLYPS analysis collected data from institutions around the world to assess if the guidelines and measures that were put into place were effective. This was an international, multi-center study that included 149 patients from 9 academic sites. In part, the analysis wanted to find how delays in treatment affected disease outcomes. The following are some of the findings:

- The vast majority of patients did not get COVID; of those who did, 26 contracted COVID from community exposure and 2 from prolonged hospitalization and subacute rehab center admission. No outpatient office-acquired infections were reported.
- 79 individuals experienced interruption in treatment and 70 had no interruption.
- A significant number of patients relapsed or progressed and 6 patients died due to disease progression.
- Individuals who experienced treatment interruption had more disease progression vs. those with no treatment interruption.
- Most of the COVID-negative patients who continued with in-hospital care, including infusions, clinical trials, ECP and phototherapy, during the height of the pandemic, had treatment interruptions. Only a small number did not experience any interruption in treatment.
- The key point: maintenance therapy is important - the pandemic experience supports developing maintenance regimens for patients with cutaneous lymphomas; there is a need for formal clinical trials of maintenance therapy.

Conclusions:

- Treatment interruptions and delays are significantly associated with negative clinical outcomes;
- Established safety protocols were effective in preventing infections during therapy for cutaneous lymphomas regardless of type of the therapy;
- Interruptions and delays in treatment regimens for patients should be discouraged;
- Clinical features for patients with COVID: patients that died were significantly older, not different from the risk factors known for general CTCL population;
- Maintenance protocols are important for outcomes;
- There were no CBCL patients included in the data;
- There was no difference in terms of COVID contraction or COVID outcomes with therapies.

CTCL & Pregnancy

There is much that is unknown about cutaneous lymphoma and pregnancies.

- Pregnant patients are rarely seen and there is sometimes conflicting data within the small number who are.
- An interaction between MF and pregnancy is seen in the increase in Th2 cytokine profile especially towards the 2nd and 3rd trimester. It is also seen in advanced MF/SS which could be a progression in pregnancy.
- There is a need for prospective clinical research including monitoring patients during pregnancy. One small study did find some early deliveries but all healthy babies.

Racial differences in clinical presentation and outcomes in MF/SS in the U.S. - a large single center retrospective analysis

Black patients with mycosis fungoides and Sézary syndrome (MF/SS) have inferior survival and distinct clinical presentations compared to non-black patients in large registry studies from the United States. The goal of the analysis was to characterize the differences in presentation, treatment and outcomes to identify drivers of disparities among black patients with CTCL.

The following are some of the reported findings:

- The experience of black patients is poorly studied in this disease due to lack of racial/ethnicity data in prospective cohort studies, lack of representation in clinical trials and tumor banks;
- There are limits to current data
 - misdiagnosis or missing diagnosis and poorly defined treatment groups
 - time of symptom onset to diagnosis is not known
- CTCL is more common in black patients, who present at younger age, and black females predominantly present with higher stage disease.
- Race remains significant for survival in patients less than 60 yrs old;
- Hypopigmented patients had improved outcomes;
 - 10 year survival of hypopigmented at 100% and almost exclusively found in black patients;
 - young, black non-hypopigmented patients appear to have inferior survival;
- black patients had an increased risk of progression and several other higher risk features including higher tumor stage, nodal stage, increased LDH, but had no difference in survival in the overall patient group.

U.S. study of extracorporeal photopheresis (ECP) in varying MF & SS stages:

Race-based differences in treatment utilization and response - Single center study

- The available data suggests that black patients present with more advanced stage disease at younger age and that black women present at younger age than white counterparts.
- The rate of disease progression or response to treatment is unknown for black patients.
- There is a gap in knowledge regarding significance of race in treatment of CTCL using ECP. A study that looked at black patient utilization of ECP and outcomes, identified 42 patients over the past decade (slightly higher number of women) and showed no significant difference of black patients receiving ECP;
- There is lag in starting ECP treatment between black and white patients.
- The duration of response to ECP treatment was shorter in black patients.

Further investigation with a larger prospective patient group to study the outcomes and impact for this patient population and ECP is needed.