

CUTANEOUS LYMPHOMA RESEARCH

As you dive into the following pages and the incredible research done by the recipients of this year's Young Investigator Awards and Catalyst Grants, we hope you will take great pride in our investment on your behalf.

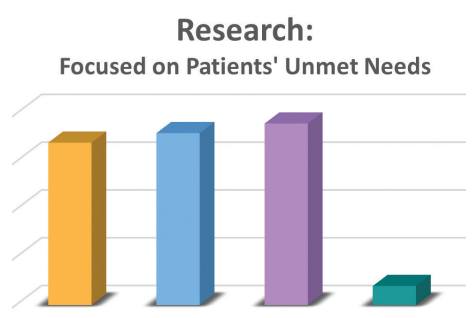
This year marks the beginning of a new strategic plan, which we are finalizing and will share soon. The Foundation's Board of Directors and Research Advisory Council continue to look toward the future to ensure that we make the most of our donors' funding and how we represent your voice in research - ultimately providing the most significant impact in advancing cutaneous lymphoma care.

Strategy 3 of the plan, is written as: *advance research and patient care focused on tackling the most important unmet needs of people with cutaneous lymphoma.* As we work to achieve this strategic objective, we continue to seek opportunities to support the pillars outlined in the Cutaneous Lymphoma Research Roadmap while adding one more, Pillar 4, Quality of Life.

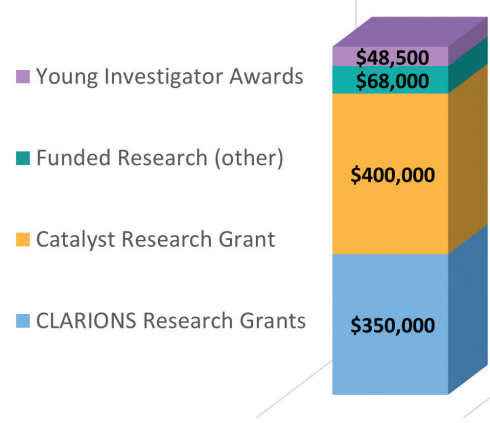
The Foundation has always had a strong interest in helping the broader community understand the impact of cutaneous lymphomas on people living with it. Dating back to the early 2000s, we funded the very first quality-of-life study in cutaneous lymphoma with Dr. Marie-France Demierre. We continue to be a visible participant across all areas addressing access, drug development, and clinical advancement, serving as a patient opinion leader.

More and more, a top priority among clinicians and drug manufacturers, and a requirement by policymakers and regulators, is including the patient's experience. This resulted in the addition of Pillar 4: Quality of Life - gathering patient-reported lived experience on how cutaneous lymphoma impacts their life.

We hope you are excited about how far we have come - investing nearly \$900,000, funding 19 research projects, and supporting 33 young researchers - and the vision of hope for the future to meet the most critical needs of people impacted by cutaneous lymphoma.



- | Pillar 1: Why Did I Get Cutaneous Lymphoma?
- | Pillar 2: What Cutaneous Lymphoma Do I Have?
- | Pillar 3: How Do I Treat My Cutaneous Lymphoma?
- | Pillar 4: How Does Cutaneous Lymphoma Impact Quality of Life?



2023 Issue 1 - Research Edition

Advance research and patient care focused on tackling the most important unmet needs of people with cutaneous lymphoma

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What Is Cutaneous Lymphoma?

Cutaneous lymphomas are cancers of lymphocytes (white blood cells) that primarily involve the skin. Classification is based on lymphocyte type: B-lymphocytes (B-cell) or T-lymphocytes (T-cell). Cutaneous T-cell lymphoma (CTCL) is the most common type of cutaneous lymphoma that typically presents with red, scaly patches or thickened plaques of skin that often mimic eczema or chronic dermatitis. Progression from limited skin involvement is variable and may be accompanied by tumor formation, ulceration and exfoliation, complicated by itching and infections. Advanced stages are defined by involvement of lymph nodes, peripheral blood, and internal organs. ❧

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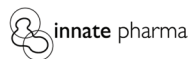
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Disclaimer

The Cutaneous Lymphoma Foundation does not endorse any drugs, treatments or products reported in this newsletter. Information is provided for informational purposes only. Because the symptoms and severity of cutaneous lymphoma vary among individuals, the Cutaneous Lymphoma Foundation recommends that all drugs and treatments be discussed with the reader's physician(s) for proper evaluation, treatment and medical care.

The Cutaneous Lymphoma Foundation's patient educational newsletter, Forum, has been made possible in part thanks to the following generous supporters:



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FROM THE BOARD PRESIDENT AND CHIEF EXECUTIVE OFFICER

Laurel Carlson, Board President; Susan Thornton, CEO

Somewhere in the world, someone in a lab is working to figure out answers.

Paraphrased from a presentation by cutaneous lymphoma specialist,
Dr. John Zic, Vanderbilt University Hospital.

When discussing research in cutaneous lymphoma, we love to share the above quote from Dr. John Zic. It is true. As your representative at the various scientific and medical meetings worldwide, we have the privilege of listening to the outcomes of work being done in labs and clinics by incredibly dedicated people. The treatment toolbox and methods of managing the wide range of cutaneous lymphomas come from this intense work in the petri dish and every day in the clinic.

This Forum focuses on research projects we have funded. It gives a small glimpse into the work necessary to learn more about this complex group of diseases. It is a pleasure to share with you the wide variety of projects on the following pages, all of which are valuable pieces to putting together the cutaneous lymphoma puzzle.

While you may not have a research or scientific background, we hope the brief articles are informative and inspiring. For all of us living with cutaneous lymphoma, know that there is someone in a lab with the light on working hard on your behalf somewhere in the world.

Sometimes progress is painfully slow and meticulous. Know that every nuance uncovered in a research project helps to add another piece to the puzzle.

Progress is happening!

Enjoy the updates, and know that there is always hope!

Laurel *Susan*



Laurel Carlson



Susan Thornton



TOGETHER AGAIN!
2-DAY PATIENT CONFERENCE
FRIDAY EVENING, APRIL 21, 2023 -
SUNDAY NOON, APRIL 23, 2023

The annual 2-Day Patient Conference is open to anyone affected by cutaneous lymphoma. Regardless of where you are in your journey, the conference is an opportunity to learn more about living with cutaneous lymphoma.

Visit www.clfoundation.org/Bethesda2023 or use the QR code to learn more.



CUTANEOUS LYMPHOMA

2022 CATALYST RESEARCH GRANT RECIPIENTS

QUALITY OF LIFE IN PATIENTS WITH CUTANEOUS T-CELL LYMPHOMA: VALIDATION OF A NOVEL QUALITY OF LIFE INSTRUMENT

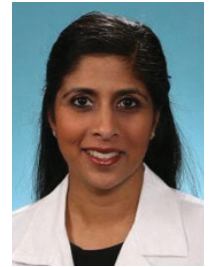
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Cutaneous T-cell lymphoma (CTCL) is a rare cancer that mainly affects the skin, blood, and lymph nodes. It is a particularly unique cancer in that it causes significantly debilitating symptoms. Studies have shown that CTCL has a negative impact on patient quality of life even more so than patients with other skin conditions requiring similar treatment. We have found this is due to its unique symptoms, treatments, and psychosocial burden on the people affected. Given this, it is important to have a way to evaluate CTCL patients’ quality of life in a meaningful, comprehensive, and disease specific manner. Though there are many surveys available to evaluate quality of life, we have found that the existing surveys do not

encompass all themes important to CTCL patients, particularly for those with advanced stage disease. This can be seen in the accompanying table. We have therefore set out to create a new survey that fully encompasses all themes important to CTCL patients, that will be made employing the voice of the patients themselves.

Table 6 Patient concerns identified by our patients with cutaneous T-cell lymphoma (CTCL), as addressed in existing quality-of-life (QoL) instruments

| | HUI3 | SF-36 | Skindex | DLQI | MF/SS-CTCL |
|---|------|-------|---------|------|------------|
| Itch | | | * | * | |
| Pain | * | * | * | * | |
| Fatigue | | * | * | | * |
| Sleep | | | * | | |
| Skin breaks (fissuring, sores, lacerations) | | | * | | |
| Skin flaking | | | | | * |
| Lack of understanding in community | | | | | * |
| Concern about appearance | | | * | * | |
| Isolation | * | * | * | * | * |
| 'Otherness' | | * | * | | * |
| Depression | * | * | * | | * |
| Hopelessness | | | * | | * |
| Uncertainty | | | * | | * |
| Treatment burden | | | * | * | * |

QoL instruments assessed included the Health Utilities Index Mark 3 (HUI3), RAND 36-Item Short Form Health Survey (SF-36), Skindex-29 (Skindex), Dermatology Life Quality Index (DLQI) and the mycosis fungoides/Sézary syndrome-CTCL (MF/SS-CTCL) QoL instrument.^{13-15,17,19}

Thus far, we have conducted interviews with CTCL patients treated at Washington University in St. Louis and analyzed what themes are most important to their quality of life. From this data we have created a new survey that intentionally has multiple questions surrounding certain themes so we can trial different ways to word similar themes, and see how different patients answer them. Since writing this new survey, we have done extensive cognitive interviews with a small group of patients in order to discuss the wording, format, answer choices, and themes included in our survey, similar to a focus group. During these meetings, we received feedback on how to make the survey clear, easier to understand, and comprehensive. They were given the opportunity to tell us which questions were more or less relevant, as well as give input if there were themes that they felt were not fully covered. From the excellent feedback we received from our patients, we have re-written our new survey. One notable observation that came up repeatedly was how different the patient experience with quality of life was in patients with early versus late stage disease. Patients with later stage disease expressed how much their quality of life has been negatively affected in all domains

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including symptom burden, sleep, hopelessness, etc. This further highlights the importance of including patients in all stages of disease in survey creation, something that has not been done in prior survey creation.

Our next step will be to distribute our survey along with other previously existing surveys in order to analyze its performance. From this data, we will be able to further consolidate the questions in our survey so only the best and best combination of questions is used in our final product. Our ultimate goal is to distribute this survey to multiple institutions in order to ensure our survey holds up in other patient populations besides our own. Eventually, we hope that this survey could be used as an additional tool to accurately evaluate, and thereby properly address, quality of life specifically in patients with CTCL, as well as be used in clinical trials to better understand the impact of treatment on patients. ❖

REPURPOSING ATOVAQUONE, AN FDA-APPROVED ANTIMICROBIAL, FOR THE TREATMENT OF CUTANEOUS T-CELL LYMPHOMA

Cosmin Tegla, MD

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Department of Medicine, Division of Hematology and Oncology
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As reported by Dr. Tegla in a recent interview with the Foundation, the aim of his research project is investigating the therapeutic potential of atovaquone as a novel agent for the treatment of CTCL. Atovaquone is an FDA-approved antimicrobial that has been used for over 20 years for the treatment or prevention of malaria, PCP pneumonia, toxoplasmosis or babesiosis. It is a safe drug with a good track record. Our preliminary data shows that the atovaquone effectively blocks the proliferation of malignant CTCL cells and specifically inhibits the viability of the malignant CTCL cells with little impact on the normal T-cell counterparts. The hypothesis of this study is that atovaquone blocks a specific vulnerability of the metabolically rewired malignant cells.

The aims of Dr. Tegla's project are to define the metabolic changes that are induced by atovaquone treatment to help determine what this underlying vulnerability is, and to determine the mechanism of action of atovaquone by using a genome-wide CRISPR cast screen aimed at identifying key effector genes.

Atovaquone could become a new therapeutic option for the treatment of CTCL because of its current FDA-approved status. Because it's a safe drug, it could easily benefit patients with early stage disease where the whole treatment goal is to minimize interventions while maximizing quality of life. At the same time, it could benefit patients with advanced stage disease where the goal of treatment is to maximize responses and duration of remissions. In either situation, atovaquone could easily be combined with the standard of care to help improve outcomes with minimal safety concerns.

In the long term, this project would help identify novel therapeutic targets in CTCL and perhaps other malignancies that share similar biology. Based on our preliminary findings, atovaquone targets CTCL in a novel and unique way. Elucidating its mechanism of action could lead to new therapeutic strategies in CTCLs and potentially have a broader impact on other malignancies that have similar biologies. ❖

To view Dr. Tegla's full interview, visit https://youtu.be/z_UwhRmsRVc

CUTANEOUS LYMPHOMA

2021 CATALYST RESEARCH GRANT RECIPIENTS

MECHANISTIC INSIGHTS INTO THE CD39/CD73 ADENOSINERGIC IMMUNO-SUPPRESSIVE AXIS IN PATIENTS WITH SÉZARY SYNDROME: ASSOCIATION WITH DISEASE COURSE AND TREATMENT RESPONSE



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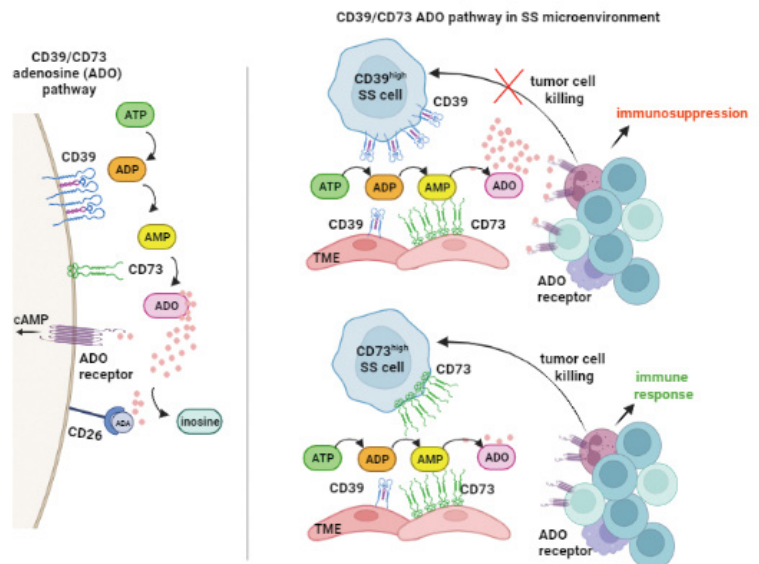
Sézary syndrome (SS) is an aggressive primary cutaneous T-cell lymphoma characterized by malignant cells circulating in the blood and progressive impairment of the immune response. No curative treatments are available so far. Immunotherapy seems to be a promising avenue to achieve long-term disease control; however, relapses are frequent with only few patients achieving long-term remissions. This is due to the ability of tumor cells to exploit different strategies to escape the host’s immune responses. A key hallmark of SS is severe progressive T cell immunodeficiency, which contributes to increased risk of infections that are the most prevalent cause of death in patients with advanced disease. What is coming into focus is that the malignant T cell is a key driver of immunosuppression, reshaping the cutaneous microenvironment and broadly impairing cellular immunity, which is needed for an effective anti-tumor response. Understanding how tumor cells escape from immune surveillance and how past and emerging therapies can modulate the immune system is the starting point for the development of more effective multimodal and combination therapies. Emerging as a relatively new immune checkpoint is the production and accumulation of immunosuppressive metabolites in the tumor microenvironment.

Project objective:

To investigate whether the sequential activity of CD39 and CD73 ectoenzymes - highly expressed by malignant T cells as well as by immune cells and vasculature – might scavenge ATP released by apoptotic cells and generates immunosuppressive adenosine in the tumor microenvironment thus contributing to tumor escape from immune response and immune dysfunctions in patients with SS.

Milestones:

- i) In our study we demonstrated aberrant expression of two proteins (namely, CD39 or CD73) in malignant T cells circulating in the blood and infiltrating the skin in SS patients. Both proteins are key players in the generation of immunosuppressive adenosine from ATP, an energy-carrying molecule released from dying and stressed cells. Adenosine is a potent immunosuppressive mediator promoting tumor intrinsic or therapy-induced immune escape by various mechanisms.
- ii) The expression of these two molecules allowed us to identify two subgroups of patients with high expression of CD39 or CD73, respectively. Patients showing high CD39 expression proved to be characterized by a highly immunosuppres-



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sive microenvironment dampening the immune response against the tumor.

iii) In experimental conditions recapitulating the situation occurring *in vivo*, we demonstrated that using specific drugs able to block the functions implemented by CD39 or CD73 thus inhibiting the adenosinergic pathways, has the potential to unleash an immune-mediated anti-tumor response.

These findings suggest that modulating cancer-derived adenosine in the tumor microenvironment is an attractive novel therapeutic strategy to limit tumor progression, improve antitumor immune responses and avoid therapy-induced immune deviation.

While what will be the most effective therapeutic regimen for SS patients remains unclear, the current trend appears to be combination therapy able to eliminate the disease via effective killing of immunosuppressive tumor cells, coupled with activation and education of the immune system to generate a potent anti-tumor immune response. Through better understanding of various immune modulating pathways, superior combination therapies may be developed, and prolonged remissions realized, eventually improving the quality of life for patients. ❖

Additional Research Credits: Ada Funaro, MD, PhD, Department of Medical Sciences, University of Torino, Italy

H-1PV-INDUCED ONCOLYSIS AND TUMOR MICROENVIRONMENT IMMUNE STIMULATION IN A NOVEL HETEROTYPIC SPHEROID MODEL OF CUTANEOUS T-CELL LYMPHOMA

The project focused on a novel approach to cutaneous lymphoma treatment, namely the use of a “good” (so-called oncolytic) virus that is able to kill cancer while sparing healthy cells. The oncolytic parvovirus H-1 (H-1PV) has long been shown to be a promising therapeutic agent against a variety of solid tumors such as glioma and pancreatic cancer. However, H-1PV potential to become a new weapon in the fight against cutaneous lymphoma was never studied before, and was first made possible through the Catalyst Research Grant of the Cutaneous Lymphoma Foundation. For the sake of better relevance to patients’ situations, a novel *in vitro* (spheroid) model was developed, with the aim to reproduce tumor complexity *in vivo*. Studies in this model led to the generation of first preclinical data that strongly encouraged further research on H-1PV as a candidate drug for the treatment of cutaneous lymphoma.

Briefly, while being innocuous for normal blood cells, this

oncolytic virus was able to kill cutaneous lymphoma cells and to cause significant shrinkage of lymphoma spheroids. The killing effect – oncolysis - was independent of the expression of cellular pro-survival proteins (Bcl-2), but might be boosted by purinergic receptor (P2X7) activation and signaling. In addition to oncolysis induction, parvovirus infection of tumor cells triggered the release of danger associated molecules (in particular, extracellular adenosine triphosphate) that may alert the immune system of the host to the presence of parvovirus-infected lymphoma cells. Furthermore, when lymphoma spheroids were co-cultured with human peripheral blood cells, H-1PV treatment caused the secretion of inflammatory mediators such as tumor necrosis factor-alpha and increased spheroid infiltration with immune cells. The capacity of the virus to induce efficient immunogenic death of cutaneous lymphoma cells deserves further investigation and holds promise for the development of a novel therapy against this disease. ❖

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CUTANEOUS LYMPHOMA

2022 YOUNG INVESTIGATOR AWARD RECIPIENTS AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING

BLOCKADE OF THE IMMUNE CHECKPOINT CD47 BY TTI-621 POTENTIATES THE RESPONSE TO ANTI-PD-L1 IN CUTANEOUS T CELL LYMPHOMA

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Assistant Research Professor
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Background

Blockade of PD1/PD-L1 (NCT03011814) and CD47/SIRP α (NCT02890368) have shown promising and durable therapeutic outcomes in cutaneous T-cell lymphoma (CTCL), but resistance and/or relapses are seen in a subset of patients. To improve outcomes of immunotherapy regimens for CTCL patients, we investigated the effects of dual CD47 and PD-L1 blockade as a strategy for targeting both the innate and adaptive immune system.

Methods

We performed RNA sequencing, gene expression deconvolution (CIBERSORT) and flow cytometry analysis to assess the immune cell composition, and CD47, SIRP α and PD-L1 expression in 45 CTCL patient samples and CTCL cell lines. CTCL specimens at baseline and during treatment with anti-CD47/SIRP α (TTI621) and anti-PD-L1 (durvalumab) were used to analyze immune cell gene expression. We performed functional assays utilizing our macrophage and CTCL cell line culture systems to assess macrophage polarization, phagocytic activity of macrophages against CTCL cells, T cell-mediated cytotoxicity using a chromium release assay, and CTCL cell line proliferation before and after CD47/SIRP α (TTI-621) and anti-PD-L1 antibody (durvalumab) treatment.

Results

Our data showed that CTCL cells and CTCL cell lines over-express CD47 and PD-L1 compared with healthy control

cells, and overexpression of CD47 and PD-L1 was associated with high MYC expression in CTCL cell lines. CIBERSORT analysis of CTCL samples compared to healthy control indicated that the fraction of M2 tumor-associated macrophages (TAMs) was increased, while M0/1 were significantly lower. Our NanoString data showed decreased M2 genes, immature DC-related genes, the NK cell inhibitory receptor related genes, and up-regulation of M1 genes and the NK cell stimulatory receptors associated genes for CTCL patients after treatment with TTI-621 compared to baseline. In vitro, treatment with TTI-621 increased the phagocytic activity of macrophages against CTCL cells and enhanced CD8+ T-cell-mediated killing. Moreover, TTI-621 synergized with anti-PD-L1 (durvalumab) to reprogram M2-like tumor-associated macrophages to M1-like phenotypes by inhibiting MYC expression. Simultaneous exposure to TTI-621 and anti-PD-L1 inhibited growth of CTCL cell lines more potently than either antibody alone. RNA sequencing analysis indicated these effects were mediated by cell-death-related pathways, such as apoptosis, autophagy, and necroptosis.

Conclusions

Collectively, our findings demonstrate that CD47 and PD-L1 are critical regulators of the immune microenvironment in CTCL and that dual targeting of CD47 and PD-L1 may potentiate anti-tumor responses in CTCL. ❖

Additional Research Credits: Xiwei Wu^{3,4}, Yate-Ching Yuan^{5,6}, Hanjun Qin^{3,4}, Chingyu Su^{1,2}, Jasmine Zain⁷, Oleg E Akilov⁸, Steven T. Rosen^{2,7}, Mingye Feng^{2,9}, Christiane Querfeld^{1,2,7,10}

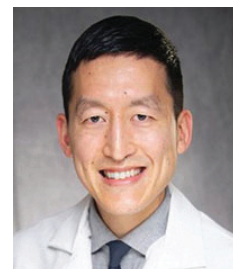
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RESEARCH GRANT UPDATES

CLINICAL CHARACTERISTICS, TREATMENT PATTERNS, AND OUTCOMES OF CYTOTOXIC CUTANEOUS T-CELL LYMPHOMAS

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Introduction

Cytotoxic cutaneous T-cell lymphomas (CCTCLs) are an uncommon group of neoplasms defined by expression of at least one cytotoxic marker (e.g. TIA-1, granzyme B, or perforin). Due to their rarity, comparatively little is known about their presentation and overall course. Here, we present a detailed retrospective experience of patients with CCTCLs, focusing on their clinicopathologic and molecular characteristics, treatment details, and survival outcomes.

Methods

The Stanford University Cutaneous Lymphoma Database was queried to gather data on patients with CCTCLs seen between 1995-2020, including the following diagnoses: subcutaneous panniculitis-like T-cell lymphoma (SPTCL), primary cutaneous $\gamma\delta$ T-cell lymphoma (PCGDTCL), primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (PCAECTCL), and unclassified CCTCLs (CCTCL-NOS). Clinical and laboratory data, including clinical suspicion of hemophagocytic syndrome (HPS), were extracted from the electronic medical record. Treatment data were recorded, including use of radiotherapy (RT), pralatrexate, romidepsin, brentuximab vedotin (BV), combination chemotherapy, allogeneic stem cell transplant (allo-SCT), and others. We evaluated time to next treatment (TTNT), calculated as the start date of one line of therapy to the start date of next line of therapy, in addition to overall survival (OS) and factors predictive of outcome. A subset of patients was evaluated with a clinically validated high-throughput sequencing panel for hematopoietic and lymphoid neoplasms (Heme-STAMP) covering 164 genes.

Results

46 patients were included: 22 (47.8%) SPTCL, 13 (28.2%) PCGDTCL, 3 (6.5%) PCAECTCL, and 8 (17.3%) CCTCL-NOS. Mean age at diagnosis was 55.7 years (range: 14.9

– 87.4). Most patients (87%) presented with generalized skin lesions, while involvement of lymph nodes (22.2%), viscera (8.9%), or bone marrow involvement (3.1%) were uncommon. Clinical suspicion for HPS was noted in 23 (50%) patients.

Median lines of therapy received was 2.5 (range: 1-12). Median TTNT (mTTNT) from first-line therapy was 8.5 months, second-line 5.3 months, and third-line 7.8 months. Variation in mTTNT was observed between CCTCL subtypes. In patients with SPTCL, mTTNT from first and second-line therapy were 10.2 and 24.0 months, respectively. In patients with PCGDTCL, mTTNT after first-line therapy was 11.1 months, decreasing sharply thereafter (0.5-3.1 mo. for 2nd-5th lines). Patients with PCAECTCL had short mTTNT of less than 3 months for all lines of treatment. Patients with CCTCL-NOS exhibited more heterogeneity (mTTNT 2.9 – 9.1 mo. for 1st-5th lines).

The most commonly used treatments were combination chemotherapy (n=24 instances, mTTNT 7.2 mo.), pralatrexate (n=18, mTTNT 11.6 mo.), romidepsin (n=17, mTTNT 2.4 mo.), RT (n=16, mTTNT 3 mo.), and BV (n=11, mTTNT 3.7 mo.). Median TTNT varied between CCTCL subtypes and was generally longest in patients with SPTCL.

2- and 5-year OS were 73.5% and 64.2%, respectively. Significant differences were observed between CCTCL subtypes (**Figure 1 - page 10**). Age > 60 was associated with worse survival (2-year OS 42.3 vs. 100%, $p < .0001$). Extracutaneous involvement was not associated with outcome (2-year OS 60.6 vs. 69.1%, $p = 0.5$), nor was documented clinical suspicion for HPS (2-year OS 82.2% vs. 64.8%, $p = 0.21$). Patients undergoing allo-SCT (n = 9) had superior OS (2-year OS 100% vs. 66.1%, $p = 0.03$) (**Figure 2 - page 10**).

Continued on page 10...

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Continued from pg 9...

Thirteen (28.3%) patients had data available from Heme-STAMP testing; every patient who underwent testing had at least one identified mutation. The most frequently occurring somatic mutations included TP53 (n = 3), TERT (n = 3), and JAK1 (n = 3).

Conclusions

CCTCLs are rare entities with heterogeneous presentation, response to therapy, and survival. Chemotherapy remains an effective treatment, and we identify pralatrexate as a promising single agent option. Allo-SCT offers curative potential in eligible patients. Given wide variation in disease behavior, treatment intensity should be tailored to each individual’s clinical phenotype to optimally balance risk and benefit. Further efforts to define the molecular basis of CCTCLs are urgently needed to aid in the identification of more effective therapies. ❖

Additional Research Credits: Sebastian Fernandez-Pol, MD, PhD³; Shufeng Li, MS⁴; Youn H. Kim, MD⁴, and Michael S Khodadoust, MD, PhD^{1,4}.

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Figure 1. Overall Survival by CCTCL Subtype

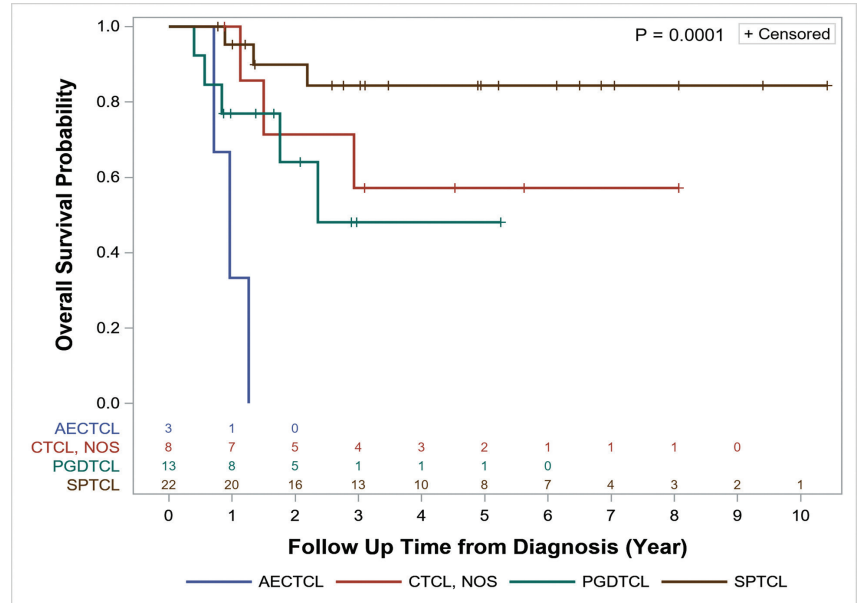
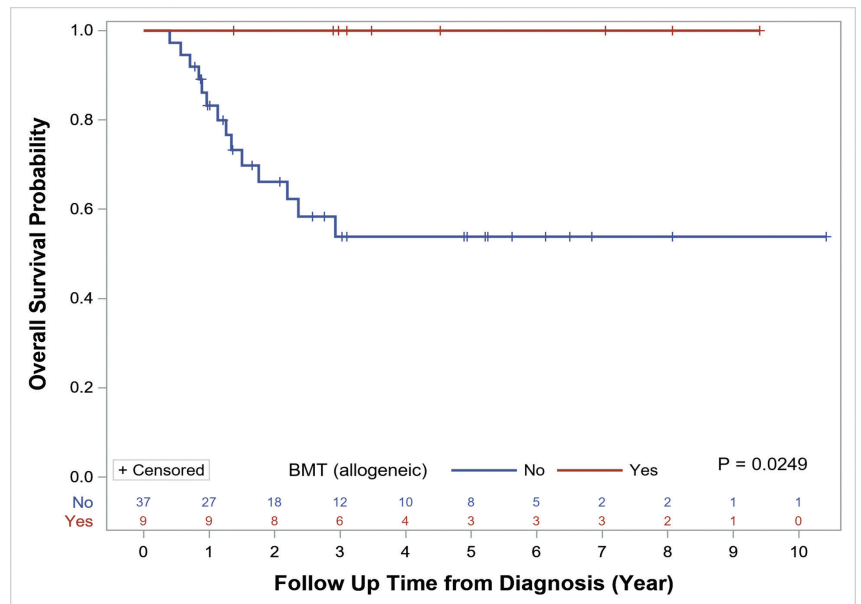


Figure 2. Overall Survival by Patients Receiving Allogeneic Transplant Versus Remainder of Cohort



RESEARCH GRANT UPDATES

2022 YOUNG INVESTIGATOR AWARD RECIPIENT SOCIETY OF INVESTIGATIVE DERMATOLOGY (SID) ANNUAL MEETING

ROLE OF p38 β IN CUTANEOUS T CELL LYMPHOMA

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Cutaneous T cell lymphoma (CTCL) is an incurable cancer; understanding its underlying molecular mechanisms may unlock a cure. In patient samples of CTCL, we observed a significant increase in gene expression of p38 β while that of p38 α decreased, compared to normal healthy CD4 T cells. This prompted us to further dissect the role of p38 β in CTCL to inform the application of small molecule inhibitors that specifically target p38 β . Current well-developed small molecule p38 inhibitors target both p38 α as well as p38 β , as they share ~80% structural similarity. However, multiple clinical trials have shown adverse effects and development of drug resistance when patients with cancer are treated with potent p38 inhibitors alone. Such side effects likely occur because p38 α is an essential protein in many cell types; indeed, p38 α gene knock-out mice exhibit embryonic lethality. Therefore, any prolonged treatment using p38 α inhibition may cause adverse effects. Using Hut78 CTCL cells in which we silenced p38 β using lentiviral siRNA, we tested for possible mechanisms of drug resistance that could explain why patients who

participated in p38 α / β inhibitor clinical trials experience adverse effects. Gene silencing of p38 β in Hut78 cells did not decrease cell proliferation; instead, proliferation slightly increased compared to that of WT cells. This aligned with increased IL-17 RA and p38 γ which is a driver for cell proliferation in Hut78 cells. Our hypothesis is that p38 β -depleted CTCL cells increase survival by elevating the MAPK12-NFAT-IL17 signaling pathway axis, which increases proliferation and propagates inflammation in the surrounding regions resulting in drug resistance and adverse effects. We used confocal immuno-fluorescence microscopy analyses of p38 β -depleted Hut78 cells to reveal a novel molecular mechanism, in which depleting p38 β offset cytoskeleton formation in the cytosol. This suggests p38 β is important for maintaining the shape or frame of CTCL cells, and may explain why CTCL, a malignant T cell infiltrate skin, from which novel revenues of drug development may be invented that are complementary to p38 β inhibition. ❖

Additional Research Credits: Sangkil Nam¹, Jack Hsiang¹, Steven Rosen¹

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