Celebrating Advances in CLL Research

By Michael J. Keating, MB,BS

The last several years have yielded impressive progress in the development of more effective and targeted treatment options for CLL patients. These developments have in turn resulted in improvements in patient survival rates, and the positive trajectory continues through 2018. Thanks to a better understanding of the pathophysiology of CLL, including the identification of multiple proteins that are integral to the evolution and survival of CLL cells, we are finally seeing major shifts in therapeutic options that are available to CLL patients, along with a concomitant improvement in patient outcomes. Though still described as incurable in medical schools, there is mounting evidence that, for an ever-expanding patient population, long-term remissions in CLL patients are achievable.

The current status of CLL is considered to have commenced in 1983 when fludarabine was found to be effective for the management of relapsed and refractory CLL. The evolution of fludarabine-based treatments inspired the fludarabine-cyclophosphamide-rituximab (FCR) regimen, which has now been approved as the standard of treatment in the United States and around the world for patients less than 65 years of age in relatively good physical condition. We now have long-term survival data from patients who received FCR. A review of the original 300 patients treated in the Phase II FCR study shows a high rate (60%) of very long-term (12.8 years), disease-free survival in those patients with mutated immunoglobulin heavy chain variable (IgVH) gene who do not have abnormalities in chromosomes 17 or 11 (1). These results support the continued use of chemoimmunotherapy outside of clinical trials in fit patients who meet these criteria.

The next major breakthrough to occur in CLL therapeutics came with the discovery of several proteins integral to CLL development and survival, including Bruton’s tyrosine kinase (BTK), phosphoinositide 3-kinase delta (PI3Kδ), and B-cell lymphoma 2 (BCL2). Having identified them, researchers next developed small molecule inhibitors targeting these specific proteins, blocking their actions, and inhibiting the disease. These inhibitors include ibrutinib, idelalisib, and venetoclax, respectively. Results from a recent Phase II study in young, fit, high risk CLL patients combining the BTK-inhibitor ibrutinib with FCR (iFCR) showed the regimen induced deep responses, with 57% of participants achieving a complete response (CR) with bone marrow minimal residual disease negativity (BM-MRD-neg) and 83% of participants achieving BM-MRD-neg (2). These results are significantly higher than the 20% rate of response seen in this population with FCR alone.
In those patients for whom FCR is not recommended, whether based on age, fitness level, or the molecular characteristics of their disease, major therapeutic breakthroughs using the small molecule inhibitors including ibritinib, idelalisib, and venetoclax, and monoclonal antibodies such as rituximab and obinutuzumab, now provide numerous treatment options. Recent updates from multiple trials using these agents in combination are showing response rates as high as 90-100%.

Early results from an investigator-initiated study combining ibritinib with venetoclax in previously untreated, high-risk CLL patients revealed promising results, with all patients who completed at least 3 months of the combined therapy showing either a partial or complete response (3). An interim analysis of results from the randomized, Phase III MURANO trial evaluating the benefits of venetoclax plus rituximab (VR) versus bendamustine plus rituximab (BR) in patients with relapsed or refractory CLL showed a profound improvement in progression free survival at 24 months in the VR treatment group (84.9%) versus the BR group (36.3%) (4). As reported at the 2018 American Society of Hematology meeting, regimens that combine ibritinib and venetoclax, with or without a monoclonal antibody, are producing complete response rates of 80% after one year or more of therapy. This is good news for older patients, as well as for those who have deletions in chromosomes 11 or 17 and/or unmutated IgVH. These findings indicate the doctrine of CLL as an incurable disease may soon be overturned.

The ever-increasing treatment options available to even high-risk and relapsed/refractory patients make this a unique and exciting time in CLL research. Your continued support of our mission to abolish CLL as a threat to the life and health of patients ensures that CLL Global Research Foundation is able to remain at the forefront in support of many of these activities, translating the optimistic early information into programs that have benefits for present day CLL patients.


---

**CANCER ADVANCE OF THE YEAR: CAR-T CELL THERAPY**

The American Society of Clinical Oncology named Chimeric Antigen Receptor (CAR) T-cell therapy as their Advance of the Year. With this therapy, a patient’s own T-cells (a type of white blood cell) are removed from the blood. The T-cells are engineered to specifically target cancer cells and then grown in the lab to produce millions of these specialty cancer-killing cells. Once expanded, the CAR T-cells are infused back into the patient to fight their disease. In 2017, the Food and Drug Administration (FDA) approved two CAR-T cell therapies targeting acute lymphoblastic leukemia and diffuse large B-cell lymphoma. In addition, clinical trials using this technology in CLL, as well as several solid tumors, are underway in hospitals across the country. As these trials progress, clinicians are developing a better picture of how to optimize this new technology to treat CLL, and how to identify those patients with the greatest chance of responding to CAR-T cell therapy. CLL Global has had the fortune to fund several research projects examining this adoptive cell immunotherapy. You can read more about this exciting advance at https://www.asco.org/.
Research Highlights from Down Under

In 2017, CLL Global Research Foundation funded an ambitious three year research program, the “Center of Research Excellence in Chronic Lymphocytic Leukemia at the Victorian Comprehensive Cancer Centre (VCCC)”. Headed by Dr. Constantine Tam of the Peter MacCallum (Peter Mac) Cancer Centre and the University of Melbourne, this research program seeks to expand on the major advancements that have occurred in the treatment of CLL. We provided an overview of the program in our 2017 newsletter. Here, Dr. Tam gives us an update on the tremendous progress the team has made in just their first year.

“This grant has been running for approximately 12 months. In the last 6 months, we have further proven the usefulness of circulating DNA in a project involving the use of combination ibrutinib and venetoclax in patients with mantle cell lymphoma, a disease related to CLL. This project also discovered a new way cancer is able to escape combination targeted therapy. The work is now accepted for publication in Nature Medicine. Along a similar theme, analysis of samples collected and stored with support of CLL Global has identified a new mechanism of resistance to venetoclax in patients with CLL. This work is currently under peer review. Finally, Dr Thompson at MD Anderson and our group have established a collaborative research project extending the circulating DNA technology to patients treated with novel combination treatments for CLL at MD Anderson. In the work on BTKi-related heart toxicity, we have now recruited 32 (of a target 40) patients for our clinical study of heart function before and during BTKi therapy. In the work on BTKi-associated bleeding, Professor Jackson is extending her studies to a larger number of patients starting BTKi at our hospital to confirm her preliminary findings of differential platelet effects between ibrutinib and zanubrutinib, which is a more targeted version of ibrutinib with potential for reduced side-effects. Other projects including analyses of serial genomic and immunological changes during novel agent therapy continue to progress on track”.

INVAC-1 Clinical Trial

In a first for CLL Global, this year we are partnering with Invectys Cancer Immunotherapeutics, a biopharmaceutical company based in Paris and focused on the development of innovative cancer therapeutics, to fund a Phase II clinical trial testing their INVAC-1 anti-cancer DNA vaccine in CLL patients. A Phase II clinical trial is designed to assess how effective a particular treatment is at reaching a pre-determined endpoint, in this case achieving minimal residual disease (MRD)-negative status. INVAC-1 targets a protein called telomerase which is overexpressed in many cancers including CLL. Results from a Phase I study in solid tumors indicated that INVAC-1 is a safe and potentially useful immune therapy. The Phase II study will look at two different groups of CLL patients; 1) untreated, high-risk patients with early stage disease, and 2) patients receiving treatment with ibrutinib. In addition to monitoring the primary goal of achieving MRD negativity in both patient groups, patients will also be monitored for improved immune function and the development of second cancers. We look forward to sharing updates on this trial with you as it progresses.
HIGHLIGHTING OUR PATRONS

FLY FOR A CURE: THE EYAD KARKOUTLY LEUKEMIA LYMPHOMA RESEARCH FOUNDATION

Susan Karkoutly, Founder and President of the Eyad Karkoutly Lymphoma Leukemia Research Foundation, is one of our inspired benefactors. To date the Eyad Karkoutly Lymphoma Leukemia Research Foundation has hosted three “Fly for a Cure” kite flying festivals at the Spirit Ranch in Lubbock, Texas, raising $60,000 to support CLL Global’s clinical research and patient education initiatives.

To find out more about what inspired Susan to create the Foundation, and where she got the idea to use kite flying as a way to fundraise, we reached out to her for an interview.

1. You started the Foundation in honor of your son, Eyad, who succumbed to CLL in 2014. Can you tell us a little about him? What is one of your favorite memories from his life?

Eyard was a joyful and kind soul, and I treasured every minute I spent with him. He always made me so proud. Throughout his life, he was admired by his friends, teachers, colleagues, and everyone he encountered for being polite, creative, smart, and genuine. He placed his heart into everything he did, including his legal career, friendships, and authentic love for music. On top of his beautiful smile, comical sense of humor, and musical talents, he was also a celebrated film buff. Even when he was suffering from intense pain, he managed to fill his hospital room with the sounds of laughter, vintage music, and classic movies, and spent long hours joking with his wife, Amanda, family and friends.

2. You have had great success with your two Fly for a Cure fundraisers. What gave you the idea for a kite flying event? Are you planning to continue to host future events?

I wanted to create a family-friendly fundraising event that could involve the community more, and was inspired to incorporate kite flying activities after a trip to the beach in California. We liked the idea of hosting an event where families and children could fly kites, listen to music, and enjoy other outdoor activities together, while still supporting our efforts to fundraise for a cure.

3. You have donated some of the money you’ve raised to CLL Global Research Foundation to fund CLL clinical research. What led you to decide to support CLL Global?

We were looking for an opportunity to support the advancement of pioneering CLL research, and we were happy to learn about the ways the CLL Global Research Foundation has led globally in treatment option development for CLL patients and were happy to donate to benefit their cause and continued research. Dr. Michael Keating has also been a great advocate and support for our own foundation and regional efforts, being so kind as to attend our fundraising events to share information regarding research advancements.

Dr. Keating addresses attendees of this year’s “Fly for a Cure” fundraising event.
4. In addition to the Fly for a Cure events, are there other mechanisms you have for raising money and bringing attention to the Eyad Karkoutly Lymphoma Leukemia Research Foundation?

Our foundation primarily exists in West Texas, and is still in its early stages of outreach, but we have managed to raise awareness and community support through social media promotion, local sponsorship, and commercial radio advertising through the local TTU KTTZ-FM NPR station.

5. Is there anything in particular you would like our readers to know about the Eyad Karkoutly Lymphoma Leukemia Research Foundation, or Eyad himself, that we have not already discussed?

From the very beginning of his diagnosis, Eyad never stopped fighting or let his fear overcome his kindness. His ongoing faith, generosity, and positive spirit are what gave him strength, and continue to give us strength everyday. I try my best to relay his positive energy and strength in the foundation’s efforts, and in my daily life.

What I’ve learned most from this experience, is that anyone who loses someone to cancer can, in fact, channel their pain into strength to help others, and join in the fight to find a cure.

—Susan Karkoutly

YELLOW JACK: A NOVEL BY RENE UZEE

At CLL Global we are continually amazed by the energy, creativity, and talent of our patrons. One of these is CLL patient and author Rene Uzee who recently published Yellow Jack, a story about the 1853 Yellow Fever epidemic in New Orleans, Louisiana. The book delves into the catastrophic effects the epidemic had on the city, and the political corruption and scandal that followed, a story that ends in a current-day courtroom. Yellow Jack is the culmination of 15 years of work put forth by Rene, during which time he experienced homelessness and unemployment due to flooding from hurricane Katrina, followed shortly thereafter by a CLL diagnosis. Despite these “bumps in the road” Rene persisted in his research and saw his dream come to fruition in 2018 with the publication of his book. Rene and his wife Brenda are long-time benefactors of CLL Global. In their customarily generous fashion, Rene and Brenda are donating proceeds from the sale of all Yellow Jack merchandise to CLL Global. If you are interested in a fascinating read, as well as supporting a wonderful cause, you can find more information at yellowjackbook.com.

Dr. Michael and Rene Uzee sporting their Yellow Jack t-shirts. *All proceeds from the sale of Yellow Jack merchandise benefit CLL Global Research Foundation.
**SURVIVORSHIP MATTERS**

CLL is the most common type of adult leukemia in the Western world, and it is estimated that 20,490 new cases of CLL will be diagnosed in 2018. Thanks to effective new treatment options available for patients that require therapy and the often indolent nature of the disease, most patients with CLL have a long life expectancy. Due to this longevity, patients with CLL are susceptible to co-morbidities, the second most frequent of these being other cancers (OC). CLL patients have an increased incidence of OC compared to the general population, occurring at a frequency as high as 36% of patients. The most common OC diagnoses are non-melanoma skin cancer, prostate cancer, breast cancer, melanoma of the skin, and lung cancer. Because of the increased risk for developing a second cancer, it is advised that CLL patients be vigilant about preventative care and screenings. Based on an extensive literature review and the consensus of a multidisciplinary team of physicians, an algorithm has been established with these recommendations. CLL Global is committed to patient education and cancer prevention. We are currently working to secure funding to establish a CLL Survivorship Clinic, helping to ensure that patients are following the recommended screening and vaccination guidelines, and to recommend patients to additional services when needed. Are you up to date?

### Cancer Screenings

- Annual skin exam for skin cancer prevention and education on sun exposure risks and sun protection strategies
- Colorectal cancer screening with colonoscopy every 5 years for individuals older than 50 years of age
- Lung cancer screening with annual low-dose thin slice multidetector CT of lungs if >30 pack- years smoking history (current or former smoker)

**Male patients:**

- Prostate cancer screening with PSA and digital rectal examination (every 1-4 years depending on age and results)

**Female patients:**

- Breast cancer screening with yearly clinical breast exam (age 25-39), annual breast exam and mammogram (age >40)
- Cervical cancer screening with liquid pap test and HPV testing every 3-5 years

### Immunizations

- Pneumococcus vaccines PCV13 followed by PPSV23 at least 8 weeks apart. Then PPSV23 booster every 5 years
- Tetanus diphtheria every 10 years
- Annual influenza vaccine (high-dose killed vaccine by intramuscular injection)
- Zoster vaccine (recombinant, adjuvanted), two doses 2-6 months apart

### Travel and Household Members

- Consideration of the Hepatitis B vaccination
- Prior to traveling, review requirements for vaccinations and avoid live attenuated vaccines
- Household members should have an annual influenza vaccine

CONGRATULATIONS TO DR. KEATING!

The Giants of Cancer Care® program recognizes individuals who have achieved landmark success within the global field of oncology. Recipients of the award are selected by their peers for their outstanding achievements in oncology research and clinical practice. CLL Global’s very own president and CEO, Michael Keating, MB, BS, was inducted into the 2018 class of Giants®. Dr. Keating was recognized for his role in the development of the chemotherapy regimen fludarabine plus cyclophosphamide (FC) and FC plus rituximab (FCR), revolutionizing CLL treatment and improving patient outcomes, and for developing cytogenetics predictive of response to treatment and survival in acute leukemia. Please join us in congratulating Dr. Keating on this prestigious and well-deserved honor.

Cancer greats Dr. Michael Keating and Dr. Emil Freireich celebrate Dr. Keating’s 75th birthday.

HAPPY BIRTHDAY DR. KEATING!

In addition to celebrating Dr. Keating’s Giants of Cancer Care® induction this year, we also celebrated his 75th birthday. In recognition of this momentous occasion several of the greatest minds in CLL clinical and basic research came together to show their appreciation for having had the opportunity to mentor, be mentored by, and work alongside Dr. Keating over his 40+ year career at MD Anderson Cancer Center located in Houston, Texas. Notable among those offering accolades was his mentor, Dr. Emil Freireich, a pioneer in clinical oncology research who, along with his longtime collaborator Emil Frei, M.D., developed the first combination chemotherapy treatments shown to be effective against childhood leukemia. In addition to recognizing his clinical achievements, Dr. Keating was also recognized for his unwavering commitment to his patients’ health and physical, mental, and emotional well-being. Please join us in wishing Dr. Keating a happy birthday, with many more to come.

Still have some last minute shopping to do? Check off names on your gift list and support CLL Global at the same time. Visit the Amazon Smile website (https://smile.amazon.com) and select CLL Global Research Foundation as your beneficiary. For all eligible purchases, the AmazonSmile Foundation will donate 0.5% of the purchase price to CLL Global.
**THINGS TO COME**

The New Year promises to be a positive and productive one for CLL Global and the CLL community. We are continuing our partnership with Patient Power – a Cancer Community on a virtual webinar series “Understanding CLL: Guidance for Accessing the Best Care”. The first two webinars in the series, “Understand the Ins and Outs of Watch and Wait”, and “Genetics 101: Everything You Need to Know About Genetic Testing and CLL” have been produced and can be re-watched on the Patient Power website (www.patientpower.info/chronic-lymphocytic-leukemia). Three additional webinars are planned for 2019. The webinars offer an opportunity for a live question and answer session with CLL experts from around the United States. Registration (free!) information on the 2019 webinar will be made available on the Patient Power website and on the CLL Global Facebook page once they are scheduled.

Additionally, our first international research conference of the year, “Celebrating CLL Therapeutic Advancements”, is scheduled for January 25-27, 2019, in Houston, Texas. Over 30 CLL experts from around the world will come together to participate. We are also looking forward to reviewing preliminary results from the INVAC-1 clinical trial, and will share these with you once available. And of course we anxiously anticipate hearing from the 12 investigators who recently received research funding from CLL Global. Please keep in contact with us throughout the year, either through our quarterly electronic newsletter, our Facebook page, or our website, so that we can provide you with the latest and greatest from CLL Global and the CLL community.

**HAPPY NEW YEAR**

CLL Global Research Foundation would like to take this opportunity to wish everyone a joyful holiday season and a prosperous and productive New Year. We are profoundly grateful for your continued support, and are committed to putting your contributions directly into groundbreaking CLL research and patient support endeavors. Over 90% of our annual expenditures go directly towards these priorities. The upcoming year holds great potential to bring more, improved treatment options for CLL patients. We look forward to sharing these exciting best practice advances with you throughout the year.

---

**CLL Global Research Foundation:**

**OUR MISSION IS TO ABOLISH CLL AS A THREAT TO THE LIFE AND HEALTH OF PATIENTS BY ACCELERATING CLL RESEARCH.**

Please consider making a donation today and help us turn our passion for finding a cure for CLL into a reality for patients around the globe. To donate online please visit our website at cllglobal.org/donate.

Donations may also be mailed to CLL Global Research Foundation, P.O. Box 301402, Unit 428, Houston, Texas 77230.