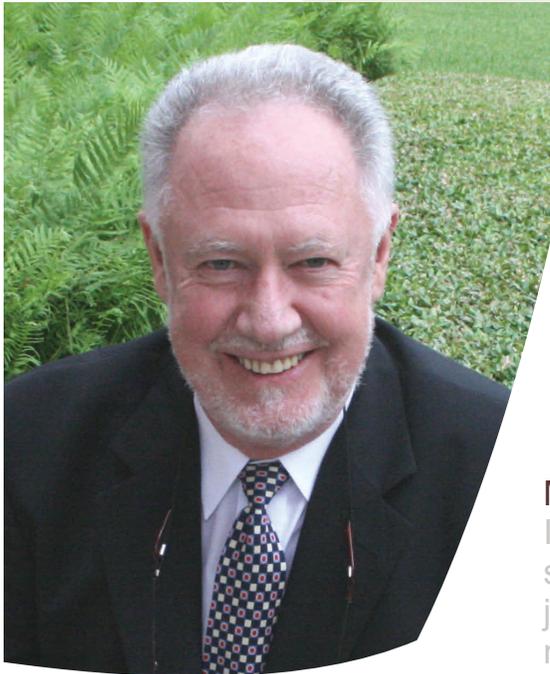


President's *Corner*

REPORTS AND OPINIONS FROM DR. MICHAEL KEATING
ON THE HAPPENINGS OF THE CLL RESEARCH WORLD



Getting Rid of Chemotherapy in CLL: **a magical mystery tour**

My experience with CLL has been a trip of a lifetime. I have been optimistic about eradicating this disease since day one, and former skeptics are finally jumping on board. So come with me now for the magical mystery tour of CLL and learn how we are changing the way patients are treated....

Chemotherapy has played a pivotal role in cancer treatment for many decades. My mentor, Dr. Emil J Freireich, led the first clinical trials using multiple types of chemotherapy as treatment in the 1960s. The success of these experiments led to the cure for 80-90% of patients suffering from childhood acute lymphoblastic leukemia, opening the door to combination chemotherapy as a standard option for most cancers.

Twelve years ago, we combined two chemotherapy drugs, fludarabine (Fludara) and cyclophosphamide (Cytosan), with the monoclonal antibody, rituximab (Rituxan). This combination, known as FCR, changed the way CLL is treated and has had a significant impact for CLL patients. It has become the standard treatment option for patients who can tolerate it, and has been described as “The gold

standard for CLL”. While this sounds good, concerns have persisted.

Fludarabine and cyclophosphamide, and all chemotherapies, cause suppression of the immune system, a depression in normal blood counts and DNA damage which may contribute to the causation of second cancers. Additionally, FCR and other current treatments are not benefiting every CLL patient. Thus, a major goal regarding treatment is to replace chemotherapeutic agents with more personalized options.

The anti-chemotherapy era in which we are about to embark has been decades in the making. One of the biggest challenges to date with treating CLL is that it has a very comfortable relationship with other cells in the body and the immune system. Even though

CLL is an invader, the body thinks it is not. CLL cells manipulate other cells in order to stay alive and thrive. Previously, researchers could not figure out why some drugs worked well when tested in a petri dish in the laboratory, but were significantly less effective once given to patients. Once this mystery was partially solved, the playing field changed.

Researchers have found a way to interrupt the relationship between CLL cells and the surrounding cells (called the microenvironment). An important line of communication in this relationship is the B-cell receptor signaling pathway. There are several molecules involved in the communication, and disrupting these molecules is proving very effective. The inhibitors of the B-cell receptor signaling pathway currently being tested in clinical trials are GS-1101 (formerly CAL-101) and ibrutinib (formerly known as PCI-32765). These are given as oral agents.

By disrupting the B-cell receptor signaling pathway, the CLL cells are released from their microenvironment in the lymph nodes, spleen and probably the bone marrow. The white cell count initially goes up before subsequently declining to levels below where the white cell count started. In some cases, particularly when these inhibitors are combined with a monoclonal antibody, we are now getting to the point where patients have no significant spike in the lymphocyte count. This is because the antibody eliminates the CLL cells as soon as they enter the blood stream. The majority of patients are tolerating the treatment very well, even those who cannot tolerate chemotherapy and older

patients up into their 80's. These drugs are currently being tested alone and together with monoclonal antibodies. This is part of the magic which is available in clinical trials at the present time.

Dr. Freireich's rationale has always been that it does not matter if you do not understand how the drug works; if it works, use it. Patients do not want to be sick. The science can be figured out later. This approach still applies today. Lenalidomide (Revlimid) is proving to be powerful for CLL patients. However, the mechanisms of the drug currently remain a mystery.

Lenalidomide is an immune modulating drug or IMiD. Like the B-cell receptor inhibitors, it changes the relationship of the CLL cells and the microenvironment. It was first introduced for the treatment of multiple myeloma. Subsequently, it was determined that lenalidomide is an active agent in relapsed patients with CLL. This discovery was initially led by Dr. Asher Chanan-Khan, currently at Mayo Clinic in Jacksonville, FL.

“The anti-chemotherapy era...has been decades in the making.”

Shortly after, Dr. Alessandra Ferrajoli, MD Anderson Cancer Center, led initiatives to use lenalidomide as a first-line treatment in older patients. Lenalidomide is now being combined with monoclonal antibodies, rituximab (Rituxan) or ofatumumab (Arzerra), which is demonstrating a superior response than either the monoclonal antibodies or lenalidomide given as a single agent. MD Anderson Cancer Center is now taking this combination of lenalidomide and rituximab to frontline therapy.

Lenalidomide is a very potent drug which has many beneficial effects on the immune system. It increases the number and activity of immune T-cells which are important in killing cancer cells and improves the production of antibodies by the normal B-cells. Because of the compromised immune system in CLL patients, antibody production is often low. This drug offers a new way of reversing this issue. While the exact mechanisms of action are not fully understood at the moment, lenalidomide has already become an important part of the CLL treatment arsenal.

Another piece of potential magic in CLL is the chimeric antigen receptor (CAR) so prominently mentioned in the press and the medical literature from a small but exciting study from UPenn. CARs will probably serve a diverse role in CLL treatment. CARs can potentially be used as intervention for minimal residual disease, which is the small amount of CLL cells that remain in a patient when he or she is considered to be in remission. These cells are the major cause of relapse in cancer. Once CARs, which are currently derived from a patient's own cells (autologous), are better understood they will likely extend or replace the stem cell transplant process which uses other people's cells (allogeneic) for the treatment of CLL.

In addition to the three classes of drugs mentioned above, there are other options becoming available. In a matter of a few years, many patients will likely be started on non-chemotherapeutic regimens that include the above-mentioned agents. Both the B-cell receptor antagonists and lenalidomide are oral agents which trump intravenous therapy. In preliminary testing, both of these

agents also appear to combine well with monoclonal antibodies. None of these agents has a major detrimental impact on elements of the immune system. None of them are chemotherapy drugs and none of them cause damage to DNA.

The best part of this magical mystery tour is that these new drugs seem to be effective regardless of many of the prognostic factors we have come to know as being important in predicting outcome. We are about to embark on a voyage where we can use agents that are simple to administer with very favorable side effect profiles and better results. While some may say I am overly optimistic, I feel this is necessary to keep the energy going to provide all CLL patients with the best treatment and the best results possible. When we finish working to eliminate this disease, 100% of CLL patients will be benefiting from the treatments available.

A. J. Krug

