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2016 Year in Review

CLL Global has provided over 24 million in research funding (2005-2016)

Curing CLL—The Big Push

by Michael J. Keating, MB, BS

CLL—A Disease Under Attack

We continue to make great strides towards finding a cure for CLL. We are now able to more accurately identify which patients are in need of therapy and which patients should delay treatment. In CLL, we are fortunate to have at our disposal a number of new potent and safe agents, new approaches to therapy, and a variety of forms of immune modulation. For the first time there is substantial evidence that a large number of patients, 1 in 3, will have a greater than 10 year failure-free survival (a continuous complete remission for greater than 10 years). However, while it is nice to see these good results, we have to remember that the hole in the donut represents patients who are not being well controlled by our present medications.

The largest group of patients for whom we have available data demonstrating outcomes are those in the so-called watch and wait category (W&W). A nomogram we developed predicts the probability of these patients needing intervention within 2-3 years. For those patients needing intervention, treatment regimens have been developed to try to achieve minimal residual disease (MRD) negativity (no detectable CLL cells in the blood or bone marrow). Previous studies in W&W patients used an ineffective chemotherapy agent, chlorambucil, with its associated DNA damage that could contribute to the development of other cancers. The current course of action includes treatment with ibrutinib and following the outcome of these ibrutinib-treated patients over time.

An additional treatment option that is in the pipeline for patients is an intriguing DNA vaccine against the enzyme telomerase. This vaccine was developed at the Pasteur Institute in Paris. It will be offered to W&W patients who show high expression of telomerase. This study group can be identified by use of the aforementioned nomogram. The goal in treating these patients is to achieve an MRD-negative state and delay the need for therapy for more aggressive CLL.

An important element directing the treatment of CLL patients is the identification of genetic changes which occur in CLL cells. The most common abnormalities identified are deletions of portions of the chromosomes 13q, 11q, and 17p. These are extremely useful in the identification of risk. It is additionally important to note that the trisomy of chromosome 12 is no longer considered to be adverse, and that patients with this genetic abnormality respond very well to

chemoimmunotherapy programs. Other adverse genetic abnormalities have been identified by next generation sequencing (NGS), including, NOTCH1 and SF3B1. Studies are ongoing to find drugs that can target these abnormalities.

How to Cure CLL

Currently, the goal guiding the initiation of treatment for CLL is the total clearance of the disease. The traditional complete remission (CR) criteria, however, are now considered to be inadequate. If patients achieve this so-called CR but still have residual disease identified in the blood and/or bone marrow by flow cytometry, they are likely to relapse. We can now identify one CLL cell in 10,000 normal blood cells (MRD positivity) using the cells' abnormal surface proteins. Interventions to attempt to eradicate the remaining CLL cells are underway using targeted therapies such as venetoclax, CAR T-cells, NK cells, and other forms of immunotherapy. Whereas the CLL cells formerly could be identified by four-color flow cytometry, now, however, six and eight color flow cytometry has increased the sensitivity, and thus our ability to predict when to initiate treatment with targeted therapies.

A number of groups are also developing plasma DNA measurements to identify the abnormal clones. This promises to give much more accurate measurements of the total tumor burden present after therapy.

All Patients Need Improved Frontline Protocols

The development of new agents and improved monoclonal antibodies provides an opportunity to explore new treatments not only for patients under the age of 70, but older patients as well. Patients with a mutation in their immunoglobulin heavy chain (IgVH) are most likely to experience a cure. The fludarabine, cyclosphamide, rituximab (FCR) chemoimmunotherapy program is most effective here, but a recently developed program of F+C together with an improved monoclonal antibody, obinutuzumab (Gayzva), plus ibrutinib has been developed. After 3 courses the majority of patients in this preliminary program have achieved MRD negativity.

Dr. Michael Keating from MD Anderson Cancer Center, Dr. Nicole Lamanna from Columbia University Medical Center, and Dr. Zeev Estrov from MD Anderson Cancer Center discuss the latest in CLL.

This is 2-4X the likelihood of achieving MRD negativity with the FCR regimen.

Patients who are unmutated, greater than 65 years of age, previously treated and relapsed are now being treated with a combination of two targeted therapies, namely ibrutinib and venetoclax. These combinations are proving to be very well tolerated with a rapid improvement in the size of lymph glands, spleen, and other sites. The promise of venetoclax to eradicate residual CLL cells from the marrow has been found to be substantiated.

Other cancers are a significant concern in CLL, namely melanoma, squamous and basal cell carcinomas of the skin, Merkel cell tumor, acute myeloid leukemia, and possible myelodysplastic syndrome in those receiving chemotherapy regimens. These targeted therapies appear to decrease the risk of developing other cancers. Identifying pre-cancerous lesions by dermatologists with appropriate initiation of treatment is important to reduce the morbidity and mortality in CLL patients.

Tumor Dysfunction

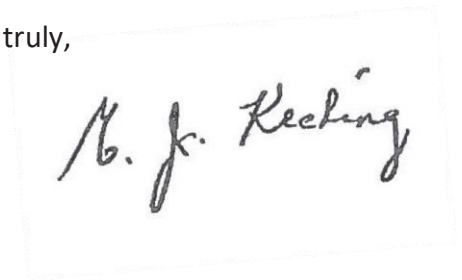
A major problem facing CLL patients is the immune dysfunction which occurs in association with the disease or as a result of treatment for the disease. Technology is now available to remove a patient's

immune cells from the blood, expand these immune cells in the lab, and then return the cells to the patient. In addition, some agents such as lenalidomide (Revlimid), have the ability to increase the T cell lymphocyte number and function in vivo. This immune restoration helps to eradicate CLL cells, which in turn helps patients develop a fully functional immune system with a decreased incidence of other cancers.

Curing CLL is no longer a pipe dream. The time is right for us to push for greater efforts towards this end. While eradication of CLL and prolonging life is crucial, the ability to have patients maintain full functionality with no increased risk of developing second cancers is a complementary goal for patients, physicians, and their teams.

(While all of us appreciate gifts, especially this time of year, many whom we serve hope and pray only for the gift of life itself. I speak for all the CLL physicians, scientists, nurses, and staff in saying that it is our honor to serve as allies with our patients in their earch to achieve this most valuable of gifts. Please join us and our patients in this effort as you contribute to organizations that support the achievement of the precious gift of life – the finest gift of all.)

Yours truly,



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