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CLL RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – A PROGRESS UPDATE

FALL 2009

ROR1: THE FIRST UNIVERSAL CLL Target Gene?

The ideal strategy for treating chronic lymphocytic leukemia (CLL), and indeed any type of cancer, is to focus therapy specifically against the cancerous cells and spare normal cells. Advances in targeted therapy therefore depend on the discovery of new molecules and targets expressed by the cancer cells but not present on normal tissues.

The recently identified molecule, ROR1, is expressed on CLL cells but not on normal white blood cells making it a perfect target for therapy. ROR1 is a receptor, or docking structure, on the cell surface to which signaling molecules can bind. Signaling molecules bind to receptors to signal the cell to start a particular function or activity such as cell division.

Because ROR1 is located on the CLL cell's surface, it is possible for therapeutic antibodies to bind to ROR1. Through research partly funded by the CLL Global Research Foundation (CLLGRF), it is becoming increasingly apparent that ROR1 plays an important role in keeping leukemic cells alive and potentially helping them multiply.

A variety of strategies including antibodies, small molecules, gene therapy and vaccines are being explored to elicit a response against ROR1.

Several monoclonal antibodies against the ROR1 molecule have been generated and are currently being characterized for functional activity against CLL cells. These monoclonal antibodies can potentially inhibit CLL cells by directly interfering with ROR1-mediated signaling that regulates their growth. Alternatively, antibodies can facilitate the destruction of the leukemia by utilizing T-cells and Natural Killer cells, the major immune cells.

Another approach to target ROR1 is to use small molecule drugs. These small molecules are medicinal compounds that have the ability to specifically bind and inhibit the biological activity of a particular cellular enzyme or component. A number of compounds that can potentially inhibit ROR1 without affecting other cellular functions are currently being screened. Together the monoclonal antibodies and the small molecules may provide new treatment options for patients with CLL.

Gene therapy against ROR1 introduces an immune receptor into T-cells that allows them to recognize, bind, and react against ROR1 on CLL cells. ROR1 is not found on normal cells; therefore, the T-cells armed with the immune receptor specifically seek out and destroy the leukemia cells with less concern for toxicity and side effects against normal tissue and cells.

CLLGRF is currently funding multiple researchers who are investigating ROR1. Dr. Häkan Mellstedt (Karolinksa Intitute, Sweden), Dr. Thomas Kipps (University of California, San Diego) and Drs. Laurence Cooper and William Wierda (UT M. D. Anderson Cancer) are evaluating ROR1 for its potential as a therapeutic target so that in the near future it can be applied in a clinical setting. : :

inside this issue:

Walking the CLL PATHWAY

Over the years I have observed that when patients are diagnosed with CLL, they start on a pathway with their disease. The pathway takes each patient through different phases based on factors of their disease and decisions that the patient makes in conjunction with their doctor about their disease. I like to break the pathway up into four phases: 1) diagnosis, 2) treatment, 3) remission, 4) relapse and re-treatment. Many patients will never go beyond the first phase of the pathway, and we always hope patients will never reach the fourth phase.

PHASE 1: DIAGNOSIS

Upon hearing a diagnosis of CLL, many patients become fearful regarding their future. However, there are simple tests which can predict the likelihood of when a patient will need treatment. The most important test apart from a simple physical examination and complete blood count is the beta-2 microglobulin. FISH, cytogenetics, and mutation status will also contribute to the decision making process and to which treatment will be most effective.

For some patients, this first phase (watch and wait) is short because they have extensive disease at diagnosis. The majority of patients will have a longer period of observation without treatment. After one year of watch and wait, it is usually clear whether the CLL will be considered progressive or smoldering (showing little signs of disease). If patients are observed for a year and have not developed extensive disease or a doubling of their lymphocyte count, they will likely have a normal and relatively healthy lifespan.

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Walking the CLL Pathway

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PHASE 2: TREATMENT

If a patient moves to the treatment phase, optimism can be generated by the fact that the majority of patients achieve a rapid and complete response. The new generation of treatments is being increasingly tailored to patients according to their specific age and the biology of their disease. There is a trend toward oral medications and targeted regimens which selectively attack leukemia cells rather than all cells. As physicians, we are constantly looking for treatments that will spare damage to the immune system as much as possible and will minimize disruption of a patient's lifestyle.

PHASE 3: REMISSION

Patients who go through the treatment phase eagerly wait to hear that they have advanced to the complete remission (CR) phase. Their excitement is partnered with anxiety over whether their disease will come back. We are now confident that we can anticipate which patients are likely to relapse.

Predictive signs include a patient's quality of response to treatment and biological factors of the disease. Many patients who respond to regimens that yield high remission rates are anticipated to be disease free for long periods of time. Treatments are being developed which will decrease the likelihood of leukemia recurrence and will help to rebuild the immune system. An important goal during remission is to remedy any damage done during the treatment phase.

PHASE 4: RELAPSE AND RE-TREATMENT

No one wants to hear that they have relapsed. However, there is increasing evidence that many relapsed patients will re-respond to the same treatment regimen which initially achieved remission. As with initial treatment, the length of these remissions is determined by the quality of response. We also look at the genetic changes that may have occurred between treatment initiation and relapse.

The CLL research community is working intensely to develop new regimens and effective drugs to benefit relapsed patients. At this phase of the pathway, physicians often consider whether a patient should undergo a stem cell transplant which can potentially cure CLL. Deciding when to transplant is crucial. Inside this issue of Momentum, you will find articles on emerging drug alternatives, options for relapsing patients and when it is appropriate to consider transplant.

Questions may still persist for you. "What path will I take? Where do I find answers?" There are a number of specialized centers for CLL around the world that can perform tests necessary to help answer some of your questions. I anticipate that within the next 3-5 years strategies to cure CLL will be in place, particularly through activating a patient's immune system and having more intelligent treatments. Our goal remains to identify the most effect treatment for each patient. Beyond that, we are working to make sure that all patients have an opportunity to enter the sometimes elusive phase of complete cure of their disease. : :

Dr. Michael Keating, Professor of Medicine at M. D. Anderson Cancer Center, serves as president and CEO of the CLL Global Research Foundation. He is an internationally renowned CLL clinical scientist dedicated to patient care and to development of potentially curative CLL therapies.

Relapse, **Rethink**, Re-treat

A portion of patients who respond to initial treatment for CLL will eventually relapse and require salvage therapy. The time to relapse can vary from within a month of treatment to years with no signs of disease recurrence.

When a CLL patient relapses, the first question to ask is whether re-treatment is immediately necessary. Some patients who relapse have indolent disease with small lymph nodes and relatively few symptoms. In such patients, the disease can remain relatively stable and may not require treatment for a long period of time (months to possibly years). One advantage of waiting is that the options for treatment may improve over time. An experienced oncologist should be responsible for deciding the right time to treat.

There are a number of factors that determine when recurrent disease should be treated. These factors include how rapidly the disease progresses, the presence of bulky lymph nodes or the presence of low red cell counts or platelets. Patients with severe fatigue, weight loss or night sweats may also need re-treatment.

Oncologists must determine the optimal re-treatment for patients, taking their individual needs into consideration. The choice of salvage therapy will depend on a number factors including response to prior treatments, complications experienced with prior treatments, general medical condition and risk of infections. Patients with good responses to prior treatment are likely to respond again.

There are numerous treatment options available to patients who relapse, and these options are growing. Options for therapy include chemotherapy-based regimens, which may be combined with a single monoclonal antibody such as rituximab, or combinations of monoclonal antibodies like alemtuzumab and rituximab. In addition, a number of newer drugs and antibodies may be available through clinical trials at more specialized centers. The article on page 4 addresses some of the new combinations under evaluation.

Some patients may be eligible for stem cell transplantation when they achieve a second response. Because the transplant itself is associated with a low, but not insignificant risk of toxicity, patients are carefully selected for this procedure. For more information on stem cell transplants, please see the article below.

Relapsed CLL can be retreated successfully in the majority of patients. Challenges for oncologists are when to treat and what treatment to use. A number of promising treatments are on the horizon. These treatments target CLL cells more specifically by engaging the immune system or by regulating genes known to help the survival of CLL cells. Through continued research, better treatments will be developed to improve the future for patients with CLL. : :

THE WHO, WHAT AND WHEN

of transplant

Many patients with CLL will never require treatment for their disease; others will respond to drugs which can extend their lifespan. A smaller number of patients will need more aggressive treatments such as a stem cell transplant. The two most common types of stem cell transplants are autologous transplant and allogeneic transplant.

In an autologous transplant, a patient's own stem cells are harvested before high-dose chemotherapy is given. The high-dose chemotherapy destroys the CLL cells, but also damages other important cells in the body, including immune cells. The harvested stem cells are transplanted back into the patient after the high-dose chemotherapy to rescue the body and to fight off any remaining CLL cells. This kind of transplant is associated with high rates of remission, but is generally not associated with better survival than is achievable with regular-dose chemotherapy. This type of transplant is performed infrequently for CLL patients.

The second type of transplant is an allogeneic transplant which uses stem cells from a donor. Similar to the autologous transplant, chemotherapy (and/or radiation) is given to a patient to reduce the CLL burden; however, the doses of the drugs are much lower. Subsequently, donor cells are introduced to the patient and they engraft and migrate to the patient's bone marrow. This provides a powerful anti-cancer effect called "graft versus leukemia effect" in which the transplanted immune cells kill remaining CLL cells. This anti-cancer activity is lacking in autologous transplants; however, allogeneic transplants carry higher risk of complications including infections.

In the past, transplants were only offered to younger (<55 years old), healthier patients. With the introduction of newer transplant procedures like mini (non-ablative) transplants, older patients up to 75 years old can qualify for transplantation as the preparative regimen is milder. This technology reduces the intense chemotherapy required prior to transplant and has also made stem cell transplants much safer.

A patient should consider a stem cell transplant for treatment of CLL if he or she is otherwise in good health and if the CLL is aggressive. Some features of aggressive CLL are a genetic alteration leading to deletion of p53 gene (also called a tumor suppressor gene), short initial response (less than 24 months) or no response to standard front-line chemotherapy, or the transformation of CLL to the more aggressive Richter's transformation.

Donor selection is a very important aspect of an allogeneic transplant. The best results are obtained with a fully matched related or unrelated donor. Results with alternative donors like haploidentical (donors with closely linked genes) or cord blood donors are also steadily improving. It is important that immediately prior to transplant a patient's disease is under good control, as outcomes with bulky or extensive disease are inferior. Currently, stem cell transplants from a fully matched donor can cure approximately 45-50% of CLL patients undergoing a transplant. : :

ROOM FOR IMPROVEMENT?

beyond FCR

As discussed in the last issue of the Momentum, the fludarabine, cyclophosphamide and rituximab (FCR) regimen has become a standard approach to initial CLL treatment. About 95% of patients who receive FCR as initial treatment will have a response.

Anywhere from 50 - 70% of patients that respond to FCR achieve complete remission (CR), meaning there is no evidence of disease in the blood or in the bone marrow. The remaining 30-50% achieve partial responses. A patient who achieves a partial response has disease status improvement but continues to have residual disease after the treatment is completed. CRs last significantly longer than partial responses. Patients who achieve partial responses have a greater likelihood of needing additional treatment; whereas patients in CR will likely not require subsequent therapy for a prolonged period of time, if ever.

Although the results with FCR are excellent, there is room for improvement to achieve and prolong CR in more patients. New drugs are being investigated for potential combination with FCR or to replace one of the existing ingredients. Initial results are already showing new combinations to be beneficial to CLL patients, including patients who become refractory to fludarabine.

Lumiliximab is an investigational monoclonal antibody. Like rituximab, it attaches to a complementary protein on the surface of the CLL cell. Rituximab attaches to a protein called CD20; lumiliximab attaches to a protein called CD23. When lumiliximab was given as a single agent to relapsed CLL patients, it caused white blood cell counts to go down and resulted in some shrinkage of the lymph nodes. There were very few side effects. Occasional mild infusion-related reactions such as low grade fever or chills were reported upon first administration of lumiliximab.

In the laboratory, lumiliximab is synergistic with fludarabine and rituximab, meaning that when lumiliximab is combined with either one of these agents the activity of both drugs is increased. Because of this synergy, a subsequent study was done combining lumiliximab with FCR in relapsed patients. The CR rate for salvage therapy in patients who have relapsed after treatment with FCR is about 25%, as opposed to 50-70% for initial treatment.

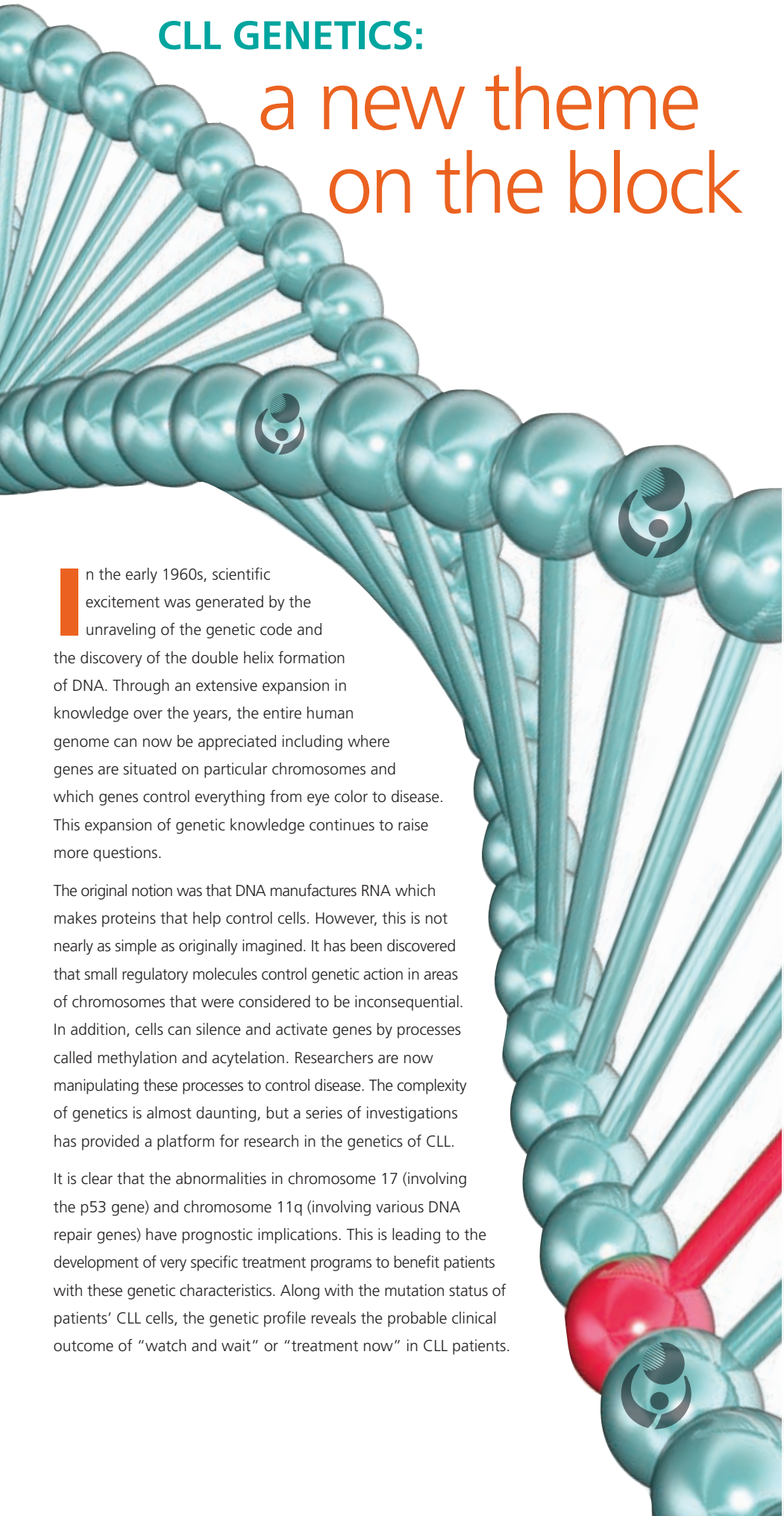
In the clinical trial, the addition of lumiliximab to the FCR regimen brought the CR rate for relapsed patients to 50%. This highly encouraging result led to a randomized trial which is currently enrolling patients in the United States and Europe. Patients are randomly assigned to the standard FCR treatment or to FCR plus lumiliximab. This clinical trial should be completed in 2010. If results are positive, the FDA may approve lumiliximab so that it can be prescribed to CLL patients outside of a clinical trial setting.

Another possible way of improving on the results of FCR is to substitute rituximab with a new monoclonal antibody that attaches to CD20 as rituximab does, but may be more effective. There are now several monoclonal antibodies like this in clinical trials. One of these is ofatumumab.

Ofatumumab has also been used by itself in a clinical trial to treat patients with relapsed and refractory CLL. As with rituximab and lumiliximab, the only significant side effects were infusion-related reactions which are generally more common with the first dose. In patients with relapsed and refractory CLL, the overall response rate to ofatumumab was about 50%. This was very encouraging given that all of the patients in this trial had received prior treatment for CLL (an average of 4 prior treatments, many with FCR) and all were refractory to fludarabine.

Based on this trial's activity, the FDA approved ofatumumab in late October 2009. The drug will soon be available to all oncologists to treat patients with CLL that are refractory to fludarabine and alemtuzumab. In addition, a trial substituting ofatumumab for rituximab in combination with fludarabine and cyclophosphomide (FCO) was recently completed with good overall response rates. A larger trial will be needed to show whether FCO is better than FCR. However, at this time FCR continues to be considered the frontline standard for younger (below age 70), more fit patients. ::

CLL GENETICS:
a new theme on the block



In the early 1960s, scientific excitement was generated by the unraveling of the genetic code and the discovery of the double helix formation of DNA. Through an extensive expansion in knowledge over the years, the entire human genome can now be appreciated including where genes are situated on particular chromosomes and which genes control everything from eye color to disease. This expansion of genetic knowledge continues to raise more questions.

The original notion was that DNA manufactures RNA which makes proteins that help control cells. However, this is not nearly as simple as originally imagined. It has been discovered that small regulatory molecules control genetic action in areas of chromosomes that were considered to be inconsequential. In addition, cells can silence and activate genes by processes called methylation and acytelation. Researchers are now manipulating these processes to control disease. The complexity of genetics is almost daunting, but a series of investigations has provided a platform for research in the genetics of CLL.

It is clear that the abnormalities in chromosome 17 (involving the p53 gene) and chromosome 11q (involving various DNA repair genes) have prognostic implications. This is leading to the development of very specific treatment programs to benefit patients with these genetic characteristics. Along with the mutation status of patients' CLL cells, the genetic profile reveals the probable clinical outcome of "watch and wait" or "treatment now" in CLL patients.

A seminal breakthrough occurred upon examining lost genetic material on chromosome 13 in CLL patients. Drs. Carlo Croce and George Calin discovered microRNA (miR) genes which have the power to silence and activate other families of genes. Their discovery has led to an explosion of miR research in the whole of cancer and is one of the leading discoveries in science in the last decade. Additional developments in the genetics of CLL have been led by researchers in Germany, notably Drs. Hartmut Döhner and Stephan Stilgenbauer.

Three major repositories exist that provide material to analyze CLL from a genetic standpoint including the German CLL Study Group (GCLLSG), the CLL Research Consortium (CRC) and UT M. D. Anderson Cancer Center. Each of these repositories has strengths and weaknesses. Rather than each repository trying to duplicate new technologies and applications, it is much more efficient to establish collaborations. This is the basis of the development of the Genetics theme in CLLGRF's U.S./European Alliance.

The Alliance already includes members from all three repositories. Based on presentations and conversations at Alliance meetings, we have decided that a Genetics theme is not only beneficial, but necessary. The investigators being recruited for this new initiative are truly top-flight. It is anticipated that initial funding for the group will be at least $500,000 per year for two years. The discoveries in this new Genetics group will likely be leveraged many-fold with further grant successes from other agencies.

The U.S./European Alliance is the perfect vehicle to efficiently develop and expand the expertise in the genetics of CLL. There are already methods being used in the laboratory to silence over- expression of important genes and replace missing genes in CLL cells. In the future, these technologies will be applied to the treatment of CLL by themselves and also in conjunction with stem cell research. The timing is right for a "perfect storm" to attack the genetics of CLL, leading to major transformations in diagnosis and a surge in treatment. : :

UNLOCKING THE CORRELATION BETWEEN

CLL and skin cancer

It is generally accepted that sun exposure increases the risk of skin cancer. Although less widely known, immunodeficiency is another major contributor. Because CLL patients are often immune deficient, they are at a higher risk of developing skin cancer as a secondary disease and have a higher risk of recurrent skin cancer. Moreover, it is likely that skin cancer will attack in a more aggressive form in CLL patients. Patients receiving treatment are at an even greater risk because their immune system is further compromised.

A recently published article written by Drs. Apostolia-Maria Tsimberidou and Michael Keating discuss the analysis of the prevalence of other malignancies in CLL patients. Data was collected on 2,028 previously untreated CLL patients seen at UT M. D. Anderson Cancer Center over a 20 year period. Among these patients, 11.2% developed other malignancies during their follow-up period. In this cohort of patients, 30% developed skin cancer, making it the most common secondary malignancy in CLL patients.

There are a number of different types of skin cancer. The most common are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC is commonly known as a rodent ulcer which burrows down into the skin but does not spread. SCC is the most frequently reported skin cancer in CLL patients. If diagnosed early enough, SCC can usually be resected without the risk of metastasis to other areas of the body such as the lymph glands.

The less common skin cancers are malignant melanoma and Merkel-cell carcinoma. These tumors, particularly malignant melanoma, are less predictable and more likely to spread than BCC and SCC. Merkel-cell carcinoma is a rare skin tumor associated with a polyomavirus. It tends to occur most frequently in people that are immune deficient, explaining its increased presence in the CLL population. Although the risk of developing Merkel-cell carcinoma is higher for CLL patients compared to the general population, from a statistical point of view, the odds are still very low.

An important element in the management of CLL is going to be the restoration of a more normally functioning immune system for patients. Modifying the immune system of CLL patients will not only help to fight the CLL, but will enhance the body's ability to prevent the development and recurrence of additional malignancies. Patients also need to be proactive in reducing their risk of skin cancer by using sun protection and taking care of their bodies so they are better capable of warding off infections and additional diseases.

The correlation between CLL and skin cancer is just starting to take shape from a research standpoint. The first step in establishing better treatment strategies is to get a better idea of the frequency of occurrence. This is being undertaken at M. D. Anderson now. A better understanding of the genetics of CLL will also shed light into this correlation. Researchers taking part in the recently established Genetics theme of the CLLGRF Alliance will help bring answers to the table (see Genetics article on page 5). ::

CLLGRF is interested in research that can provide new information regarding the relationship of CLL and skin cancer. Our goal is to support the discovery of pivotal information so that other organizations will become interested in funding research on the relationship of the two malignancies. If you would like to direct support for these initiatives, please contact us at info@cllglobal.org.

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TCL1's Relevance: NOT JUST ANOTHER ACRONYM

CLL does not behave similarly in all patients. The disease has variations that affect how it presents initially, behaves over time and responds to therapy. While a patient's clinical history and physical examination serve as prognostic markers, laboratory testing has also become an important indicator to project the clinical course of CLL and to decide upon the frequency of monitoring patients.

TCL1 is one of the more recently identified prognostic markers in CLL. It is expressed in over 90% of CLL patients, although expression levels vary. TCL1 expression levels are an indicator of how a patient may respond to treatment. A recent study conducted by Dr. Ellen Schlette and colleagues at M. D. Anderson Cancer Center showed that a high proportion of patients with elevated TCL1 failed to achieve a complete response to the FCR chemotherapy regimen. Also, this group of patients stopped responding to therapy sooner than patients with low or absent TCL1. Lastly, patients with high TCL1 had a shorter overall survival when compared to patients with low to minimal TCL1 expression.

There is also a correlation between high TCL1 expression levels and standard prognostic indicators, specifically high white blood cell counts and elevated beta-2 microglobulin. TCL1 expression was also compared to newer prognostic indicators for CLL. There was correlation between high TCL1 and unmutated IgVH genes, which has been frequently reported as an indicator of poor prognosis in CLL. When compared to another recently described prognostic indicator, ZAP70, TCL1 was superior in its predictive power for time to treatment failure and overall survival.

Extensive research by Dr. Carlo Croce and his group has shown TCL1's role in the development of CLL is important. Its role as a prognostic indicator is becoming clear, but further studies are necessary to better understand the clinical implications. ::