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RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – A PROGRESS UPDATE

SPRING 2010

FITTING GENETICS into the puzzle

The U.S./European Alliance has added a new focus: genetics. The Alliance was established by CLL Global Research Foundation to promote integrated research in CLL and to be flexible and respond quickly to potential research opportunities. After careful thought, it was determined that CLL genetics is a promising area that requires greater resources. The goal is to better understand CLL genetics and ultimately use that information to develop improved treatment strategies. To formally launch the genetics initiative, members of the Genetics working group were invited to present at the January 30-31, 2010, Alliance meeting held in Houston.

In recent years, there has been a tremendous expansion of knowledge in CLL genetics. However, much remains to be uncovered. The first break-through in this area came with fluorescent in situ hybridization (FISH), a technique that detects abnormalities on specific chromosomes. FISH enabled the identification of abnormalities in chromosomes 11 (11q-), 12 (trisomy 12), 13 (13q-) and 17 (17p-) in CLL patients. This allowed clinicians to make more customized treatment decisions for patients based off of prognosis and expected treatment outcomes. Although FISH technology has proved extremely important in regard to CLL research, other techniques that will allow a better understanding of the underlying genetics of CLL are becoming available.

FISH analysis is limited to the number of examinable chromosomes, but comparative genomic hybridization (CGH) technology looks at all of the chromosomes. The level of sensitivity in detecting abnormalities is no better than FISH analysis, but chromosomes can be evaluated which are not even looked at by FISH technology. This gives insight into previously unobservable genetic areas.

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Has the Era for PERSONALIZED CLL THERAPY ARRIVED?

During most of the last 50 years, treatment decisions for patients with CLL and many other diseases were based on the "one size fits all" categorization. Patients would usually be put on a protocol with little consideration to personalized factors of their disease. When treatment options were very limited, this approach was reasonable. Things changed, however, as new agents were approved for the management of CLL.

The challenge for any new drug is to improve upon the standard. The first cutting-edge treatment approved for CLL was fludarabine which showed a higher complete remission rate and longer remission duration than chlorambucil, the standard at the time. Fludarabine has since become an important building block for front-line therapy, salvage therapy and a primer for allogeneic stem cell transplantation.

Combination chemotherapy regimens such as fludarabine and cyclophosphamide (FC) were subsequently developed with a higher response rate than fludarabine as a single agent. More recently, chemo-immunotherapies like fludarabine and rituximab (FR) and fludarabine, cyclophosphamide and rituximab (FCR) have been developed.

FCR was approved by the U.S. Food and Drug Administration (FDA) for the treatment of CLL in February 2010. Approval was based on two large, randomized, international clinical trials, although the regimen has been used for a number of years throughout the U.S. because of initial clinical results from M. D. Anderson Cancer Center.

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EBV: Could it be a Culprit

FOR RICHTER'S IN CLL?

Up to 10% of patients who have chronic lymphocytic leukemia (CLL) will at some stage develop either non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma. This complication is called Richter's syndrome and may either be due to a transformation of the original CLL cells or development of a new clone of malignant cells.

Several studies have suggested that a virus called Epstein Barr Virus (EBV) may be involved in this complication. EBV is a common virus that infects over 95% of people. EBV infection can cause a flu-like illness (often known as infectious mononucleosis or "mono") which is usually mild and gets better when the immune system controls the infection.

Once infected, the EBV virus stays in the body for life, usually in a dormant state. However, if an individual has a weakened immune system (such as immune compromised CLL patients or transplant patients) the virus can become activated (known as Type 3 EBV). EBV can also be associated with NHL or Hodgkin lymphoma in individuals with normal immune systems (known as Type 2 EBV).

Previous studies evaluating EBV in Richter's syndrome have yielded variable results, suggesting that there may be different types of Richter's syndrome. In some cases, it may arise as a transformation from the original CLL cells. In other cases, where a patient has received intensive therapy such as fludarabine or Campath-based regimens to treat CLL, their immune system may have been weakened sufficiently to allow the virus to become activated.

Drs. Helen Heslop and Ann Leen (Baylor College of Medicine) are examining EBV antigen expression in detail. Their findings may modify the treatment options for CLL and lymphoma patients affected by EBV. For example patients with Type 3 EBV lymphomas may not need such intensive chemotherapy and may respond to approaches aimed at boosting their immune response to EBV.

Patients with Type 2 EBV will require standard chemotherapy but may be eligible for research studies where they would receive modified immune system cells called T-cells that have been specially trained in the laboratory to target the EBV proteins expressed by the tumor. For patients whose tumors do not express EBV at all, other targets, such as recently identified viruses associated with cancer and novel proteins selectively expressed on the tumor cells, can be sought. The long term goal is to offer tailored therapy to patients with this complication. : :

UNDERSTANDING THE
ABCs and 123s of clinical trials

Clinical trials can be a scary concept for cancer patients. They usually entail experimental drugs and a potentially unknown outcome. It is important for patients to understand the value of clinical trials and how they are developed. All new agents must first be tested in clinical trials. Most clinical trials are based on laboratory studies or previous clinical trials of new agents.

Before a drug can be tested in a clinical trial, it is thoroughly analyzed in the laboratory setting and results are scrutinized by institutional review boards. A protocol details precisely how the study will be conducted. A study is considered a phase I trial the first time a drug is tested in humans. A phase I trial is generally conducted at a single or a few institutions and requires a limited number of patients. This allows researchers to determine if the benefits and side effects of the drug coincide with laboratory results.

With positive results, phase I trials become phase II and then phase III trials with patient enrollment growing larger in each phase. These trials may or may not have a control or comparator arm (with a drug already proven effective). These trials can be open to multiple institutions, making the experimental agent more widely available and more easily accessible for patients. Results of these trials can sometimes be enough for federal approval, or can lead to extremely large, randomized clinical trials.

In randomized clinical trials, the investigational agent is randomized to a control arm with or without a placebo included. Randomized trials often enroll 500 or more patients who are randomly selected to receive the investigational agent, the control (standard therapy), or a placebo. Randomized trials help demonstrate to regulatory agencies and insurance carriers that a particular agent or regimen is beneficial on average to a large population of patients.

Clinical trials allow new agents to be combined with, or substituted for, established treatments. New agents undergo rigorous evaluations from clinical research committees and safety issues are continuously addressed throughout the period of a clinical trial. Strict guidelines determine whether a study will continue or be discontinued based on results that are better than or less than the pre-determined expectations when a trial is developed.

Patients often question being a part of a clinical trial and which one, if any, they may benefit from the most. It is important for patients to fully understand the risks and benefits of a clinical trial and to ask their doctor why a particular approach is the best option. Clinical trials, large and small, should be relished because they provide patients with access to the most cutting edge thinking, and they allow for patients to be proactive in curing their disease. : :

DOES A RANDOMIZED TRIAL CHANGE
the outcome?

Below you will find the results of an analysis by Dr. Apostolia-Maria Tsimberidou. Dr. Tsimberidou found that there was no difference in the fate of oncology drugs approved based on randomized vs. non-randomized studies. Two authorities on clinical research, Dr. Emil J Freireich and Dr. Kanti Rai, were invited to comment on Dr. Tsimberidou's findings.

Randomized trials are often required for the approval of drugs by the U.S. Food and Drug Administration (FDA) to ensure unbiased results for their safety and long term benefits. However, some oncology drugs have been approved based off of studies other than randomized trials.

Dr. Apostolia-Maria Tsimberidou (M. D. Anderson) and her colleagues collected and analyzed data on oncology drugs approved by the FDA from January 1973 to December 2006. The purpose of the analysis was to determine if drugs approved by non-randomized trials are as effective and safe in the long-term as those approved from randomized trials. The results were published in the Journal of Clinical Oncology in December 2009.

Between January 1973 and December 2006, the FDA approved the use of 68 oncology drugs, excluding hormone therapy and supportive care. Thirty-one of these drugs were approved without a randomized trial.

These drugs were all tested in phase I and/or II clinical trials with a median patient accrual of 79 patients, compared to the 500 or more patients generally required for randomized trials. The approval of the drugs without a randomized trial was primarily based on objective response, although other factors such as disease free survival and the improvement of symptoms were also used.

Only one of the 31 drugs approved without randomization has had approval partially revoked due to a lack of overall survival rates. None of the 31 drugs

has had approval rescinded due to safety issues. Three of these drugs are no longer recommended for their initial use because superior drugs have since been approved; these drugs have new uses and are still fully approved. In addition, 11 drugs have since been approved for subsequent indications.

Results from Dr. Tsimberidou's study are favorable for non-randomized trials and the approval of oncology drugs. The article suggests that phase II trials with definitive endpoints can result in FDA approval and that drugs approved via non-randomized trials have remained safe and effective. This analysis generates a question as to whether large randomized trials or carefully designed smaller phase II studies would optimize the use of resources. : :

Rai: THERE IS NO ABSOLUTE ANSWER

Dr. Tsimberidou deserves our thanks for reopening an issue which is critically important and yet rarely discussed. The issue, of course, is an age-old clash between scientists/clinicians. One group believes a new agent's clinical benefit can only be determined with randomized trials. The other group holds that non-randomized trials are the only way to make progress in medicine. Unfortunately, supporters on each side have become more committed to their stance over the past few decades.

One side holds that randomized trials are too expensive and take too long. This group believes that sometimes the data from randomized studies is already irrelevant by the time the results are actually reported. The other side, naturally, holds that randomized trials eliminate bias, subjectivity and therefore are the 'gold standard'.

Dr. Tsimberidou's analysis of the FDA's approval of oncology drugs over three decades suggests that both methods of trial design can work and that we should not make it an imperative that only one is exclusively correct. It leads us to accept a moderate stance: consider each drug on a case-by-case basis.

We should take stock of the potential risks and benefits: (a) the actual number of patients suffering from a certain cancer (i.e., the 'prevalence' rate) for which a drug is being considered, (b) the level and extent of, what is known in the FDA-jargon, as 'unmet medical need' for that disease, and (c) its acuity (i.e. how rapidly fatal that disease is).

For each drug, the sponsoring drug company meets with the experts at the FDA who know about that particular disease and go over the issues in advance. Then they decide whether a large randomized trial is necessary or whether one, two or even three smaller Phase II trials might be acceptable.

My conclusion is that in certain situations large, expensive but randomized trials are mandatory, while in others, smaller single-arm trials are appropriate. Dr. Tsimberidou's analysis has demonstrated exactly just that! There is no one absolute answer. Let the two methods of testing continue to be used in the future. : :

The above commentary was provided by Dr. Kanti Rai (Long Island Jewish Medical Center). The opinions stated are those of the author and do not necessarily reflect the opinions of CLL Global Research Foundation.

Freireich: RANDOMIZATION MIGHT LEAD TO DELAY

Dr. Tsimberidou has made a major contribution to our understanding of one of the important obstacles to drug approval by the FDA: their frequent insistence on prospective randomized clinical trials. As Dr. Tsimberidou and colleagues have pointed out, this technique can be powerful, efficient, and effective when used to address the proper question. Alternatively, if used improperly, it can often create misleading information, can be falsely negative and thereby greatly delay any progress in developing new drugs. More importantly, a requirement of prospective randomized clinical trials can actually present an obstacle to the development of new treatments for life-threatening diseases.

Dr. Tsimberidou has carefully reviewed the FDA approvals for the most recent 34 years, and she has identified drugs that were approved without having a randomized trial conducted. When she followed up these approvals, she discovered that these drugs proved as effective and as useful as drugs that were approved after randomized trials were conducted. This is a major contribution to our understanding and identification of obstacles

to the development of new agents for treating catastrophic illnesses, and hopefully it will add to the growing appreciation of the need for streamlining and accelerating the drug review and approval process in order to benefit our patients. : :

The above commentary was provided by Dr. Emil J Freireich (M.D. Anderson Cancer Center). The opinions stated are those of the author and do not necessarily reflect the opinions of CLL Global Research Foundation.

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As more is learned about the contributing factors of CLL, clinical trials are establishing whether particular subsets of patients can benefit from a unique treatment approach. Thus, we are entering the field of personalized medicine.

The personalization at this point is somewhat crude. The age of a patient is identified as an important prognostic factor. Older patients have been under-investigated in the past, so it is refreshing that protocols are now being written for this group. Another factor to consider is co-morbidities. Some patients have a number of other problems such as hypertension, diabetes, residual lesions from strokes, kidney failure, etc. These all have impacts on how a patient will respond to treatment.

It is apparent that genetic subgroups of patients have to be approached differently. Patients with abnormalities of chromosome 17 (17p- or p53 dysfunctional patients) are in real need of novel approaches to treatment. Most patients failing to have control of their disease in the first one to two years of treatment have a chromosome 17 abnormality.

On the contrary, it is now emerging that patients who have a relatively favorable beta-2 microglobulin or those with 11q abnormalities respond very well to therapy. Thus, one size does not fit all and one approach is not appropriate for everyone.

The ultimate personalization is to instruct a patient's own immune system to recognize their CLL cells as being foreign and to attack them. Multiple approaches are being developed, one of which uses chimeric antigen receptor (CAR) molecules that teach the patient's immune T-cells to attack the leukemic cells. Exploiting the uniqueness of patients' cells in an immune fashion will be fundamental to eradicating the leukemic cells, either single-handedly or in combination with other regimens.

We have come a long way with the "one size fits all" approach. Survival of CLL patients continues to increase incrementally over time. Patients are not only living longer but are living better with long periods of remission. We still have a lot of work ahead of us so that every CLL patient can reap these benefits, regardless of their genetic and individual factors. The true personalized approach to treatment is essential for us to go to the next level of potentially curing patients with CLL. : :

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.

FINE-TUNING CLL genetics

Researchers study the genetics of CLL by evaluating chromosomes. The chromosomes in CLL cells, as in other diseases, contain genetic abnormalities which are usually related to gains or losses of pieces of chromosomes. In CLL, the most common abnormalities include loss of part of chromosome 13 (40% of CLL patients), loss of part of chromosome 11 (10-15% of CLL patients), an extra copy of chromosome 12 (known as trisomy 12, 10-15% of CLL patients), and loss of part of chromosome 17 (4-5% percent of CLL patients).

These known abnormalities help in understanding the mechanisms underlying the development and progression of the disease and help physicians decide upon the best treatment. However, they do not completely explain the evolution of CLL. Researchers believe there are additional genetic abnormalities that are still unknown. Scientists studying CLL anticipate that a more complete list of abnormalities will increase understanding and lead to better therapies.

The currently known abnormalities were initially discovered because they were large, often affecting one-third or more of a chromosome, and therefore easy to see. Unknown abnormalities are likely to involve gains or losses of much smaller segments of chromosomes. In order to discover small segments of gain or loss, researchers are turning to a new technology called SNP (pronounced snip) genotyping.

A single nucleotide polymorphism (SNP) is a change in a single nucleotide (a small chemical building block) in the DNA sequence. This change in sequence is responsible for genetic differences from one human to another-differences that influence hair color and height, as well as the risk of developing certain diseases.

SNPs are the most common type of genetic variation. By sequencing DNA from many individuals, researchers have identified millions of SNPs among the three billion nucleotides of DNA in the human genome. Now researchers need to figure out which SNPs might be specifically related to CLL.

Using SNP microarray technology, researchers can compare SNPs of CLL patients and analyze commonalities of areas with DNA gain or loss. This gives insight to currently unknown affected chromosomes, and possibly additional areas of chromosomes already known to be involved in CLL, that may be associated with the disease. This information will allow researchers to investigate new subgroups of CLL patients regarding prognosis, treatment resistance and many other factors. The newest SNP chips contain probes for one million SNPs; in theory, this technology makes it possible to discover gains or losses that affect only 2% of a chromosome, compared to the larger abnormalities which affect up to 30% of a chromosome.

A major advantage of SNP genotyping is that researchers can evaluate gains and losses of DNA in all 23 pairs of chromosomes simultaneously. Another advantage is that it does not require cells to divide in culture. This is especially useful for studying CLL since CLL cells generally fail to divide in culture and die after a few days.

A shortcoming of SNP genotyping is that it cannot detect abnormalities in which two chromosomes exchange pieces of their DNA because there is no overall gain or loss. However, CLL is generally characterized by gains and losses of DNA making SNP genotyping a useful tool to investigate genetic changes in this disease. Stay tuned. The best is yet to come. : :

RESEARCH DOLLARS at work

Thanks to the generosity of many supporters, CLL Global Research Foundation recently funded six new projects with anticipation that these new research endeavors will lead to new tools and information to put an end to CLL.

One promising strategy to hasten the cure of CLL is to help immune cells identify bad (cancerous) cells. In order for this recognition to occur, CLL cells need to be forced to interact with immune cells. Molecules called chimeric antigen receptors (CARs) are engineered proteins on the surface of immune cells that attach to an antigen or protein on the surface of the CLL cell. This interaction allows the immune cell to recognize and destroy the CLL cell. Two recently funded grants are being utilized for projects that use CARs for immune therapy in CLL.

Drs. Laurence Cooper (M. D. Anderson), William Wierda (M. D. Anderson) and Thomas Kipps (University of California, San Diego) are developing a CAR that targets the protein ROR1, which is exclusively expressed on CLL cells. Dr. Gianpietro Dotti (Baylor College of Medicine) is developing a CAR which specifically targets the protein CD19. The CARs bind to either ROR1 or CD19, both located on the surface of the CLL cell. Once bound, the immune cell is activated to destroy the CLL cell. Dr. Cooper and Dr. Dotti are currently generating preclinical data with the goal of initiating clinical studies.

Two other recipients are analyzing the CLL microenvironment. Dr. Varsha Gandhi (M. D. Anderson) is studying the effects that the microenvironment has on Mcl-1, a protein found in abundance in CLL cells. Mcl-1 provides a survival advantage to CLL cells by inhibiting apoptosis (cell death), a normal process in the life of a cell. This causes an increase of CLL cells in the body. Dr. Gandhi is evaluating several therapeutic options that exploit pathways used by the microenvironment to increase the production of Mcl-1 in leukemia cells.

Dr. Peng Huang (M. D. Anderson) is also receiving support from CLL Global to investigate a novel compound that is highly potent against CLL cells, especially in the presence of the microenvironment. The compound, selecticine, shows minimum toxicity in normal cells. Based on these observations, Dr. Huang is investigating how the microenvironment may sensitize CLL cells to selecticine, why it is selectively toxic towards CLL cells, and also if it can be combined with other anti-CLL drugs to improve the anticancer activity.

Because each CLL patient is different, a variety of strategies will be necessary to eliminate the disease. Roughly 20% of CLL patients have a deletion on chromosome 11 (11q-). These patients often have a more aggressive form of CLL. Dr. Lynne Abruzzo (M. D. Anderson) is identifying the missing genes on chromosome 11 that may contribute to the aggressive behavior of the 11q- subtype. Once these genetic differences are determined, new therapies can be applied in an attempt to reverse the deletion of these genes. Dr. William Plunkett (M. D. Anderson, Chair of CLL Global Scientific Advisory Board) has suggested a specific new drug (sapacitabine) to exploit this genetic flaw.

During the course of their disease, about 10% of CLL patients will develop a more aggressive lymphoma known as Richter's syndrome. Epstein-Barr virus (EBV) has been reported as a possible initiating factor, but this has yet to be conclusively shown. Dr. Helen Heslop (Baylor) is working to determine whether EBV is involved in Richter's syndrome. : :

FIND OUT MORE ABOUT THE PROJECTS WE ARE ACCELERATING AT **WWW.CLLGLOBAL.ORG**

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Another new approach to investigating genetics is the use of single nucleotide polymorphisms (SNPs). This technology can evaluate the smallest genetic changes on chromosomes and gives greater discrimination as to whether genetic information is normal, lost or gained. The analysis of the results is time consuming and cumbersome but is giving clearer insights into patterns of genetic change.

CLL Global has been fortunate to be able to assemble a who's who of CLL geneticists to address all of these new technologies. Members of the new Genetics theme include: Dr. Carlo Croce (Ohio State University), Dr. George Calin (M. D. Anderson), Dr. Stephan Stilgenbauer (University of Ulm, Germany), Dr. Ulf Klein (Columbia University), and Dr. Lynne Abruzzo (M. D. Anderson).

Dr. Kevin Coombes (M. D. Anderson) will add a vital component of bioinformatics allowing large amounts of genetic information to be analyzed. His work, and the development of new tools, will allow the integration of information from multiple Alliance participants. Ultimately, the goal is to make the information easily accessible to all of the Alliance investigators.

As the Genetics group develops, the Antibodies and Minimal Residual Disease group is being down-sized. There has been little improvement in measurement of minimal residual disease. The advancement of new monoclonal antibodies is largely controlled by the pharmaceutical industry, giving very little flexibility to investigators attempting to initiate newer approaches.

Adding the Genetics theme to the Alliance is a major undertaking and would have not been possible without the financial support of key donors to CLL Global. Initial funding for the Genetics group will hopefully be between $500,000 and $750,000 per year for two years.

This group of investigators will markedly expand the understanding of CLL genetics. Knowledge from the Genetics group will enhance the work of the other Alliance groups and will have a cumulative impact on CLL and treatment strategies. : :