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• CHRONIC LYMPHOCYTIC LEUKEMIA •
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CLL RESEARCH Momentum

MOVING CLL RESEARCH FORWARD – A PROGRESS UPDATE

FALL 2006

GENE THERAPY STUDIES UNDERWAY:

Can the immune system be stimulated to control CLL?

A phase 1 study, under the direction of Dr. William Wierda at M. D. Anderson Cancer Center, is studying a gene therapy strategy to stimulate the immune system to react against leukemia cells as a treatment for the disease. The clinical trial, initiated thanks to the support of the CLL Global Research Foundation, is evaluating safety and the ability of patients' own leukemia cells to be modified to express a new protein, ISF35, that stimulates the immune system to reject the leukemia.

Patients' leukemia cells are infected with a crippled virus that carries the gene for ISF35. The virus cannot reproduce itself and cause infection and disease, but causes the chronic lymphocytic leukemia (CLL) cells to produce the ISF35 protein. The transduction takes place in a laboratory, after which the cells are washed and administered to the patient as a vaccine. The expression of ISF35 by the leukemia cells turns the cells into a vaccine to stimulate the patients' immune system to recognize and react against the leukemia cells. When the ISF35-producing cells are administered back to patients, they also stimulate other bystander leukemia cells to prepare to die.

In prior studies, Dr. Wierda and Dr. Thomas Kipps at the University of California San Diego showed that a protein ISF154 can be administered safely to patients and stimulate an immune response. A single dose of cells was well tolerated by patients. The study showed not only that this treatment can safely be given and was well tolerated but also showed indications of therapeutic benefit such as reduction in leukemia cell counts, lymph node size, and spleen size.

ISF35 is a new molecule that is potentially more potent at stimulating the immune system than ISF154. Based on a request from the Food & Drug Administration, Dr. Wierda is repeating the same clinical trial with ISF35 as was done with ISF154, which is a single infusion of cells, to demonstrate that ISF35 is safe. The study is also evaluating immune function of treated patients to (1) confirm that the treatment is working by the proposed mechanism and (2) to optimize effectiveness of the therapy.

Enrollment on this study is expected to complete by November 2006. Based on positive results of this study, a second study will be initiated examining multiple doses of ISF35 producing cells as treatment for CLL.

This current study represents the first time human gene therapy has been evaluated in CLL patients. Depending on the outcome of this and future studies, gene therapy might prove to be a novel therapeutic modality to advance treatment of patients with CLL or potentially other malignancies. ::

inside this issue:

TWO YEARS AND $2.8 MILLION

in research grants

I am happy to report that since December 2004 we have awarded over $2.8 million in research grants. These grants were made possible due to the contributions of many individuals and families that have joined our partnership to promote CLL research. Each of our grant recipients has demonstrated a commitment to advancing CLL research. We are now pleased to provide an update on several of the research projects we are supporting.

Grant recipients receive one to two years of funding. If the research is as promising as initially indicated, two years of funding should lead to other funding opportunities. The great majority of the grants will have an impact on present or future therapy. Much of the research will also lead to improved biologic understanding which will allow for individualized treatments based on the patient's genetic make-up rather than giving the same treatment to everyone.

This is indeed a most exciting era of CLL research. The development of new observations from investigators around the world has heightened awareness of our ability to change the natural history of this disease. CLL Global Research Foundation (CLLGRF) is generating fresh and vital interest in clinical and therapeutic research in this most common of malignancies. CLLGRF is now recognized as a major contributor to CLL research and will continue to play a paramount role.

I hope this edition of CLL Research Momentum provides a glimpse into the many promising CLL research projects underway. The breadth of CLL research worldwide generates personal enthusiasm that we are making a real impact on survival in CLL. Stay tuned for future issues of CLL Research Momentum and the latest progress on our funded research. ::

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.

CAN GREEN TEA BE A CLINICALLY USEFUL WAY TO kill CLL cells?

Doctors Neil Kay and Tait Shanafelt at the Mayo Clinic are evaluating whether green tea given to CLL patients will translate into a clinical benefit. Green tea or Polyphenol E is given to patients with asymptomatic, early stage CLL. From August 2005 to January 2006, eleven patients were accrued to the phase I portion of this trial. These patients have now received from 2-6 months of treatment with oral Polyphenol E. No dose limiting toxicity has been observed in the 11 patients treated to date. Reports on clinical efficacy are not yet available.

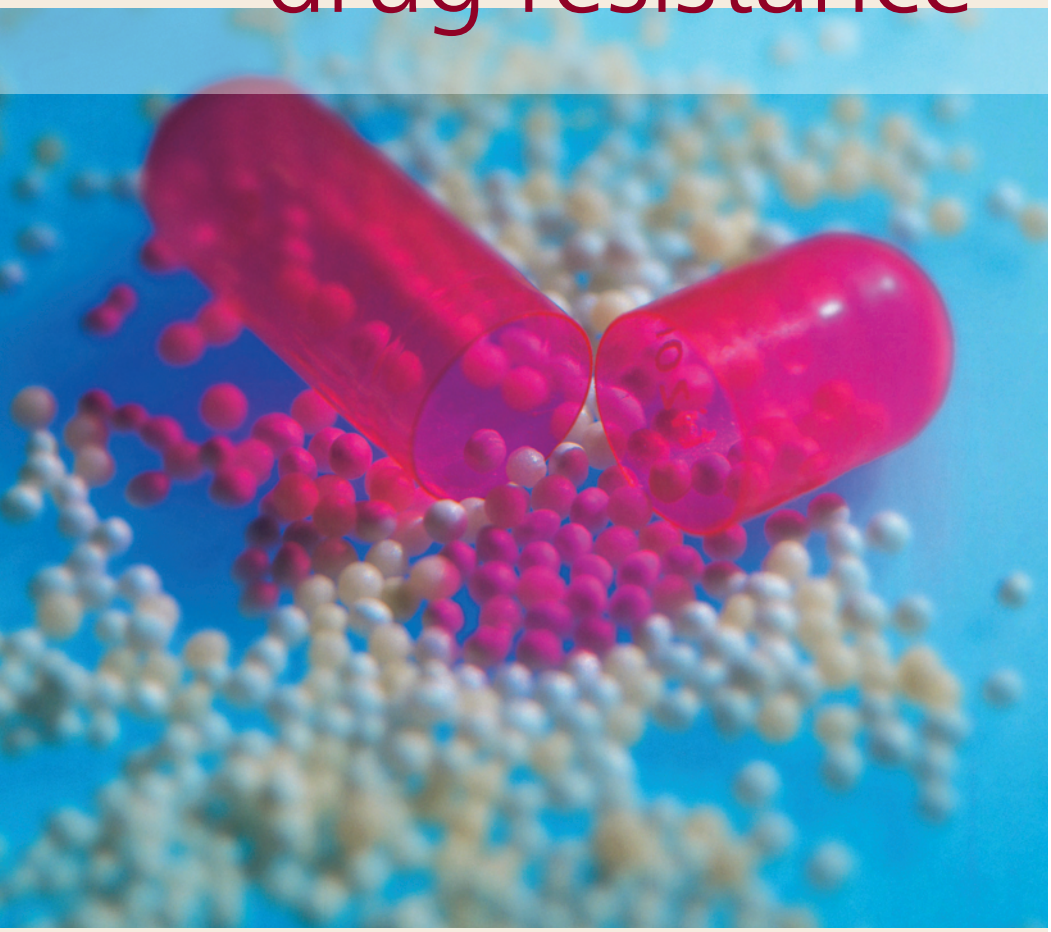
The FDA halted accrual to all human trials of green tea extracts in January 2006 due to toxicity in laboratory animals and reports of rare liver toxicity in humans taking over the counter green tea extracts. The FDA has now given permission for all green tea trials to re-open as long as capsules are administered with food and liver toxicity is closely monitored. The Mayo Clinic re-opened enrollment in May 2006 and expects to rapidly accrue to this study as they have a wait-list of 50-plus patients.

The Mayo team hopes to demonstrate previous laboratory findings that green tea extracts containing epigallocatechin-3-gallate (EGCG) will induce apoptotic cell death in primary CLL cells. The trial will determine the optimal dose and schedule of a purified EGCG in the form of Polyphenol E and will attempt to define the efficacy and toxicity of daily, oral EGCG in patients with CLL.

The results of this study may have broader relevance for hematological malignancies other than CLL. Kay and Shanafelt are currently looking at the anti-tumor activity of EGCG on non-Hodgkin lymphoma cells as well as potential combination therapies with EGCG for CLL. ::

GLYCOLYCIN SHOWS THERAPEUTIC ACTIVITY, ABILITY TO OVERCOME

drug resistance



Research by Dr. Peng Huang and his collaborators at the University of Texas M. D. Anderson Cancer Center has demonstrated that a novel compound, known as glycolycin, has potent activity against primary CLL cells. Dr. Huang and his collaborators have also shown that glycolycin is active against CLL cells that are resistant to fludarabine, a widely-used drug in frontline treatment of CLL. Recent studies in Huang's laboratory suggest that CLL cells have high frequencies of mitochondria DNA mutations, which likely cause mitochondrial malfunction and render the cells more dependent on glycolysis (glucose energy metabolism outside the mitochondria) to generate ATP (adenosine triphosphate: the cell's energy source) to accomondate the cellular energy requirements. By inhibiting the key glycolytic enzyme known as hexokinase 2, glycolycin effectively depletes ATP in CLL cells and causes the demise of leukemia cells.

Animal models are important for evaluating therapeutic activity of anticancer agents. However, Huang and other CLL researchers have difficulty using the currently available CLL animal models to test the therapeutic activity of compounds due to the slow and unsynchronized development of CLL disease in the animals. Therefore, the research team has first evaluated the activitiy of glycolycin in two alternative mouse models, ovarian cancer and brain cancer. Huang is currently testing various cell culture conditions to establish CLL cell lines. The establishment of CLL cell lines with capacity to proliferate and cause CLL in animals would provide an extremely valuable tool for the broader CLL research community, and would provide an opportunity to better test the therapeutic activity of glycolycin and the newly synthesized P-glycolycin.

Animal toxicology studies of P-glycolycin are ongoing. The results of these studies will be used to apply for an Investigational New Drug Application (IND) for P-glycolycin from the Food & Drug Administration (FDA). Once the FDA issues an IND, Huang and his clinical colleagues will be able to begin evaluating the compound in human clinical trials. : :

8-CHLORO-ADENOSINE EFFECTIVE at killing CLL cells in laboratory experiments

Many cancers are characterized by an increased rate of proliferation of cancer cells. CLL on the other hand is associated with the disruption of the cell death pathway. Because these cells do not divide, they do not synthesize DNA or go through cell replication. Hence, agents that are DNA replication—or cell division—directed do not work well for this disease.

Dr. Varsha Gandhi and her colleagues at M. D. Anderson Cancer Center are focused on developing chemotherapy that is not directed to DNA. They have determined the metabolism and mechanism of action of a new agent, 8-chloro-adenosine, in CLL cells obtained from peripheral blood of patients with CLL. Dr. Gandhi compared this drug in CLL lymphocytes and in normal lymphocytes. The data demonstrated that the drug works in a DNA independent way in CLL cells and that in laboratory experiments the drug was effective in killing CLL cells.

The next step for Dr. Gandhi and colleagues is to bring the drug into human clinical trials. She is currently working to obtain an Investigational New Drug Application (IND) for 8-chloro-adenosine from the Food & Drug Administration (FDA). The FDA has requested additional animal toxicology studies which are currently being performed. In addition to CLL, Dr. Gandhi's team has initiated investigations to identify other diseases that could benefit from the drug. The ongoing work is evaluating whether oncogenes present in multiple myeloma and chronic myelogenous leukemia could be targeted with adenosine analogs such as 8-chloro-adenosine. : :

outcomes

Dr. Paolo Ghia and his research team at the San Raffaele Scientific Institute (Milano, Italy) are exploring which proteins are expressed by CLL cells and how they can help identify patients with a poor CLL prognosis. The team is also studying the activation of some of these proteins and their use as potential therapeutic targets. Specifically, the research team is looking at the proteins HS1 and Glo I for the ability to identify such patients with high-risk disease.

HS1 has been described previously as expressed and activated in CLL cells from patients with poor prognosis of disease. Ghia and colleagues have demonstrated that this molecule is involved in the leukemia cells' shape and mobility, likely playing a role in the migration of leukemia cells throughout the body. They plan to further study whether interfering with this molecule will translate into a therapeutic effect.

The research effort has also identified several monoclonal antibodies that recognize the activated form of HS1 typically found in patients with more aggressive disease. Ghia is now studying the use of antibodies to predict clinical prognosis.

Another molecule ZAP-70 has been previously shown to be expressed in patients with more rapidly growing disease. Ghia has also shown that ZAP-70, a molecule thought to be aberrantly expressed in CLL cells, is actually expressed in all normal B cell subsets analyzed. The level of ZAP-70 expression depends on the cells' activation status. These studies may help to shed light on the mechanisms responsible for the development of CLL. : :

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INDOLENT OR AGGRESSIVE CLL - using gene expression to determine a patient's future course

Hematologists have searched for markers to predict which CLL patients will have slowly progressing disease and which patients will have aggressive disease that requires treatment in the near future. Traditional markers, such as the number of CLL cells circulating in the blood and how rapidly the CLL cells divide, have been helpful, but are not always accurate.

Recent advances in molecular biology have allowed researchers to identify and measure many genes that distinguish different types of cancer cells (for example, colon cancer and breast cancer) from their normal counterparts. In studies of CLL, researchers have identified about 200 genes that are expressed at different levels in patients with slowly progressing CLL compared to those with aggressive CLL.

Dr. Lynne Abruzzo and her colleagues at M. D. Anderson have re-analyzed the data from several studies of CLL using new statistical tests. Their results suggest that it is possible to predict whether a patient will have slowly progressing or aggressive CLL by measuring the levels of only a few of these genes. This will allow for the development of a rapid and reliable blood test to predict the nature of a patient's disease progression.

Abruzzo has used a new laboratory technique, quantitative real-time polymerase chain reaction (QRT-PCR) that measures gene expression levels rapidly and accurately. She has employed microfluidics technology to more efficiently perform QRT-PCR. This technology, requiring only a small amount of blood, miniaturizes the test so that many genes can be measured simultaneously. Her goal is to develop a rapid and reliable blood test to predict which patients will require treatment soon after they learn that they have CLL, and which patients may never require treatment. : :