

Leukemia, Lymphoma, and Multiple Myeloma: Toward a New Understanding

Statement
of
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Good morning. I am Richard Klausner, M.D., Director of the National Cancer Institute. Thank you, Chairman Harkin, Senator Specter, and distinguished Members of the Subcommittee for inviting me to speak with you about research on hematologic cancers.

Despite advances in diagnosis and treatment and improvements in patient survival, hematologic cancers continue to have a significant impact on the lives of Americans. Right now, almost 700,000 Americans are living with leukemia, lymphoma, or myeloma (LLM), and an estimated 100,000 new cases occur each year. Although mortality has declined and 5-year survival rates have increased among adults and children with certain forms of these diseases, an estimated 60,000 Americans will die of them in 2001. For all forms of leukemia, the five-year survival rate is only 46%, for non-Hodgkin's lymphoma it is 54.2%, and for multiple myeloma it is only 28%. Despite the significant decline in the death rate for children with leukemia, this disease still causes more deaths in children in the U.S. than any other disease. Furthermore, the death rates for non-Hodgkin's lymphoma and multiple myeloma are increasing at a time when death rates for other cancers are dropping. Since the 1970's, incidence rates for non-Hodgkin's lymphoma have nearly doubled, although during the 1990's the rate of increase appeared to slow. Hematologic cancers strike individuals of all ages, from children to the elderly; men and women; and all races.

What are leukemia, lymphoma, and multiple myeloma?

To understand these diseases, we must first understand the normal development of the cells they affect. Hematopoiesis is the process by which blood cells form and mature. All the different types of blood cells arise in the bone marrow from a common pluripotent hematopoietic stem cell, and undergo a series of developmental steps to differentiate into mature cells and assume specific roles in the body. New, immature blood cells may stay

in the marrow to mature or may travel to other parts of the body to mature. Normally, blood cells are produced in an orderly, controlled way, as the body needs them. Some circulate throughout our bodies via blood vessels and lymph vessels. Some reside in the lymphatic tissues that are primarily concentrated in lymph nodes, thymus, spleen, and in most of our major organ systems.

Leukemia, lymphoma, and multiple myeloma are all cancers of the blood-forming organs, or hematopoietic neoplasms. They arise due to errors in the genetic information of an immature blood cell. As a consequence of these errors, the cell's development is arrested so that it does not mature further, but is instead replicated over and over again, resulting in a proliferation of abnormal blood cells. Nearly every stage of the hematopoietic process can give rise to a distinct type of cancer.

Historically, scientists and physicians have classified these diseases by their locations in the body, the appearance of affected cells under the microscope, and the natural progression of the diseases. In leukemia, the cancerous cells are discovered circulating in the blood and bone marrow, while in lymphoma, the cells tend to aggregate and form masses, or tumors, in lymphatic tissues. Myeloma is a tumor of the bone marrow, and involves a specific subset of white blood cells that produce a distinctive protein.

Leukemia can arise in either of two main groups of white blood cell types -lymphocytes or myelocytes. Either type of leukemia can be acute, a rapidly progressing form of the disease in which the affected cells are very immature and unable to serve their proper purpose, or chronic, which progresses more slowly and is distinguished by cells that are relatively well differentiated but still function poorly. Lymphoma involves lymphocytes and can also be subclassified. Non-Hodgkin's lymphoma (NHL) is the more prevalent form of the disease. Among non-Hodgkin's lymphomas, indolent disease progresses slowly and exhibits well-differentiated lymphocytes, while the more aggressive forms are characterized by lymphocytes with far less differentiation. Hodgkin's disease, which is less common than NHL and has different clinical and epidemiological features, has historically been distinguished from NHL by the presence of distinctive cells called Reed-Sternberg cells.

Leukemias, lymphomas, and myelomas share some common features, but there are major differences among them - and there are similarities and differences within each disease group. These cancers actually represent a large number of diseases that vary significantly in their causes, molecular profiles, and natural progression. In the past decade we have experienced a revolution in the field of molecular biology that has brought new tools that are helping us refine cancer classification in terms of the molecular changes that distinguish a normal cell from a cancerous one, and draw differences between cancerous cells of different types.

This is an area of research rich in scientific promise, and the NCI has issued the Director's Challenge: Toward a Molecular Classification of Tumors, in which investigators are creating comprehensive molecular profiles of tumors using DNA, RNA,

or protein-based technologies. These profiles will be used to define more informative, and clinically predictive, molecular classification schemes for human cancers.

Moving Toward a New Understanding of LLM

A major NCI initiative, the Cancer Genome Anatomy Project (CGAP), has resulted in the cataloging of tens of thousands of human and mouse genes. The CGAP database is a unique resource that allows scientists to develop tools to perform large-scale genomic analyses to characterize tumors genetically. This genetic characterization can help explain why patients diagnosed with the same cancer differ dramatically in their responses to treatment. For example, a collaboration of scientists (including NCI scientists) genetically analyzed diffuse large B-cell lymphoma, an aggressive cancer that is the most common type of non-Hodgkin's lymphoma. For 40 percent of patients with this diagnosis, standard multi-agent chemotherapy is curative. A compelling clinical problem is to understand why the remaining 60 percent of patients succumb to this disease despite chemotherapy. Reasoning that the varying therapeutic responses of patients with diffuse large B-cell lymphoma are due to undefined molecular differences in their tumors, researchers used DNA microarray technology to define the gene expression profiles of diffuse large B-cell lymphoma samples on a genomic scale. This new technology is capable of measuring the activity of tens of thousands of genes at the same time, thus creating a molecular portrait of the cells being studied.

For this study, the CGAP was used to create a specialized DNA microarray, the Lymphochip, which is enriched in genes that function in normal and malignant lymphocytes. Lymphochip microarray analysis of gene expression in diffuse large B-cell lymphoma samples revealed that this single diagnosis actually combines two distinct diseases that differ in the expression of hundreds of genes. The two types of diffuse large B-cell lymphoma that were discovered each resemble a different type of normal B lymphocyte, suggesting that these cancers have distinct cellular origins. Clinically, patients with these two types of diffuse large B-cell lymphoma had strikingly different responses to chemotherapy. Patients with one lymphoma subtype, termed germinal center B-like diffuse large B-cell lymphoma, had a favorable prognosis: 75 percent of these patients were cured by chemotherapy. Patients with the other lymphoma subtype, termed activated B-like diffuse large B-cell lymphoma, had a poor response to chemotherapy with less than one quarter of these patients achieving a long-term remission. This study provides a clear demonstration that genomic-scale gene expression analysis can define clinically important subtypes of human cancer.

This powerful new technology is now being used to study many different types of cancers, including leukemia and multiple myeloma, in an attempt to identify disease subgroups. For example, a new project, "Molecular Taxonomy of Pediatric and Adult Acute Leukemia," will attempt to correlate the expression pattern of over 30,000 genes with treatment outcome and with cytogenetic abnormalities for both acute lymphocytic leukemia and acute myeloid leukemia. In the future, such gene expression profiling of cancer cells will be used to guide patients towards therapies that are tailored for their particular diseases.

Causes, Risk Factors, and Epidemiology of LLM

Our understanding of the causes of these diseases is extremely limited, perhaps in part due to extreme heterogeneity of the diseases and the inadequacy of the traditional classification schemes to adequately address this heterogeneity. As our knowledge base about molecular subtypes grows, we hope that we will be better able to understand the relationships between causative factors and the development of LLM.

Leukemia

The leukemias are very heterogeneous, with patterns of occurrence differing by age, sex, and racial and ethnic group. For example, highest incidence of acute lymphoblastic leukemia (ALL) is in children, ages 2-4, while chronic lymphocytic leukemia (CLL) is rare before age 30, and has the highest incidence among the elderly. Chronic myeloid leukemia (CML) has a higher incidence among African-Americans than Caucasians, while the incidence of CLL is highest among Caucasians and extremely rare in Asians.

The causes of leukemia in children and adults are largely unknown, but increased or decreased risks for developing leukemia have been associated with several factors. In an ongoing, collaborative follow-up study with Japanese investigators, NCI scientists have found strong evidence of radiation-induced risks for the acute leukemias and CML among Japanese atomic bomb survivors. NCI investigators and others have shown that radiotherapy and chemotherapy for a wide variety of diseases have been linked with moderately increased risks of acute myeloid leukemia (AML), although the benefits of treatment far outweigh the risks.

Occupational exposures to ionizing radiation and certain chemicals such as benzene have also been linked with increased risk of acute leukemia. NCI is conducting an epidemiologic study of workers in China exposed to benzene at levels lower than previously studied, to characterize leukemia rates and to determine mechanisms of action and factors affecting carcinogenicity of benzene. In addition, cigarette smoking has been associated with modest increases in acute leukemia but the evidence is not yet conclusive.

The first known human retrovirus, T-lymphotropic virus type 1 (HTLV-1), discovered at NCI in 1981, is the primary cause of adult leukemia and lymphoma arising from lymphocytes known as T cells. Certain genetic conditions can increase the risk for acute leukemia, including Li-Fraumeni syndrome, Down's syndrome, Bloom's syndrome and several other rare conditions.

Lymphoma

NCI investigators have recently reported on investigations of lymphoma incidence trends. Over the last ten years, researchers have studied the histologic types of lymphoma that are on the rise; illnesses, including other cancers, associated with lymphoma; occupational groups that may be at increased risks; and the role of genetic susceptibility. Recent research has identified several possible candidates for increasing risk including pesticides, organochlorine compounds, solvents, drinking water nitrates, and hair dyes. We are now evaluating whether these common exposures are contributing to the rise in

NHL among some populations and investigating other hypothesized risk factors such as infectious agents, medical conditions, medical treatments, and genetic factors.

There has been considerable research on the association between infectious agents and cancer. *Helicobacter pylori* is a bacterium associated with a particular rare type of lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma that arises in the stomach. Both Hodgkin's disease and non-Hodgkin's lymphoma, particularly some of the more aggressive forms, occur with increased frequency among adults and children infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. In HIV-infected patients, about one-half of all lymphomas involving a type of lymphocytes called B cells are associated with the Epstein-Barr virus, including virtually all primary central nervous system lymphomas in patients with AIDS. A new Program Announcement, in collaboration with National Institute for Dental and Craniofacial Research, is being issued to stimulate research on viruses associated with the development of lymphomas among persons who are infected with HIV. The AIDS-Cancer Cohort is studying men infected with HIV to examine interactions with various environmental exposures that may contribute to the excess risk of lymphoma. Information from this project may be of value beyond the setting of HIV, as it may yield more fundamental biologic understanding of the interplay of viruses and chemicals in the development of lymphoma. A rare type of lymphoma, called Primary Effusion Lymphoma, which arises in the lining of the lung, heart or abdomen, is tightly linked to, and probably caused by, the Kaposi's sarcoma herpes virus (KSHV). People who have both HIV and KSHV are at particularly high risk. Because viruses similar to KSHV are known to cause lymphoma in animals, efforts are in progress to identify new, lymphoma-related viruses in people.

NCI scientists are conducting very large epidemiologic studies addressing the relationship between the environment and lymphoma development. In a population-based case-control study of non-Hodgkin's lymphoma, NCI investigators, collaborating with the Centers for Disease Control and Prevention (CDC), assessed exposures to pesticides, solvents, and other factors using computer-assisted personal interviews, residential carpet dust samples, drinking water samples, and blood samples. Analysis continues, as investigators extract DNA from blood or saliva samples to assess the interaction between genetic variations and environmental risk factors.

The Agricultural Health Study (AHS) is following 90,000 healthy farmers and their family members in Iowa and North Carolina in an effort to measure their risks of developing lymphoma and leukemia. NCI and National Institute of Environmental Health Sciences launched the AHS in 1993 after previous NCI research implicated occupational exposures to pesticides in the development of lymphoma. The study assesses the risks of other cancers and diseases, as well.

A new initiative called Interlymph, coordinated by NCI and involving investigators in Europe and Australia, features a pooled and simultaneous analysis of thirteen case-control epidemiologic studies of non-Hodgkin's lymphoma. The international consortium of collaborators will examine pathology, infectious agents, family history data, genetic

factors, and methodologies needed to accurately assess possible links with the development of lymphoma.

Multiple Myeloma

The median age for diagnosis of multiple myeloma is 71 years of age. The incidence of multiple myeloma is much higher in blacks than whites, and is higher among males. Similar to incidence rates, the death rates are higher among males than females and higher among blacks than whites. This is one of the few cancer sites in which the survival rate is higher for blacks than for whites. The causes of multiple myeloma and the reasons for the racial disparity in incidence are unclear.

Some studies have suggested the role of ionizing radiation, certain organic solvents and chemicals, as well as employment in farming and agricultural occupations. In recent studies, genetic factors, low socioeconomic status (SES), and obesity have been implicated. Recent attention has also focused on viruses and other infectious agents, but their role in the etiology of myeloma remains unclear. There is growing evidence that certain cytokines and chromosomal abnormalities may be involved in the pathogenesis of multiple myeloma. These laboratory-based genetic measures need to be incorporated into future epidemiologic studies to better understand the complex relationships between genetic and environmental factors in the development of this disease.

In a recent study, NCI investigators found that low SES, whether measured by occupation-based SES, income, or education, may account for about half of the excess incidence observed among blacks. Low SES may be a surrogate for a set of negative environmental characteristics, such as poor housing, dangerous jobs, lack of access to medical care, poor nutrition, and exposure to infectious agents, all of which may have a role in this disease.

The rarity of this cancer makes it difficult to adequately investigate in a single study, so that collaborative efforts involving a variety of hematopoietic malignancies are being pursued.

New Strategies for Treatment of LLM

Therapeutic research in the treatment of patients with hematologic malignancies has made enormous progress over the past 50 years, and the NCI has shepherded this important work. Many years ago, NCI established the National Service Center to enable basic scientists to design and test chemical agents for evidence of anti-tumor activity. In addition to pioneering cancer drug screening, the NCI funded an entire preclinical drug discovery and development program. The NCI has continuously supported investigators to pursue all phases of clinical evaluation of products emanating from their own discovery and developmental efforts, and interacts with the pharmaceutical industry and academic institutions to explore their novel agents.

In the last decade, there has been an enormous investment in defining molecularly targeted agents in cancer chemotherapy. Recently we have seen some inspiring success

stories, all of them direct results of this new approach. The first evidence of a consistent gene mutation associated with a particular cancer was provided about 40 years ago by the recognition of the Philadelphia chromosome, an abnormally small chromosome 22, in chronic myeloid leukemia (CML). Some years later, researchers noted that while chromosome 22 was shortened, chromosome 9 was lengthened in CML patients, which suggested that the pieces of each chromosome were exchanged, or translocated. This observation was followed by the identification of a unique fusion gene, called bcr-abl, resulting from the translocation, and the eventual development 5 years ago of one of the first oncogene-targeted drugs, STI571 or Gleevec. This compound, which was recently approved by the United States Food and Drug Administration (FDA), is directed at the bcr-abl gene product, which is expressed in about 95% of CML patients, and in some patients with other types of cancers. Gleevec has shown remarkable promise in the treatment of chronic-phase CML, and NCI is partnering with Novartis, the drug manufacturer, to facilitate a profusion of clinical trials evaluating Gleevec in other cancers, including Philadelphia chromosome-positive ALL in adults and children. Additional trials are assessing the potential benefits of combining Gleevec with other chemotherapeutic agents. Molecular analyses of other types of leukemia have now produced the identification of more than 100 additional oncogene targets that may be accessible to similar drug development strategies.

Monoclonal antibodies are showing great promise in the treatment LLM. Among them, Rituximab, which was originally approved by the FDA in 1997 for the treatment of non-Hodgkin's lymphoma (NHL), is an antibody directed at a cell surface antigen expressed on B lymphocytes and has been shown to be effective against many types of B cell malignancies. Currently, for both children and adults, rituximab is under study in combination with other therapies, including other monoclonal antibodies, attempting to attack multiple targets on a single cell type.

In addition, NCI-sponsored studies are evaluating several new antibodies. Generally, leukemias, lymphomas, and multiple myelomas are derived from cells of the immune system and therefore frequently express antigens that are present on normal immune cells such as B-cells or T-cells. Since these proteins are not present on other human cells and are not present on the stem cells that give rise to normal B-cells and the T-cells, the antigens are excellent targets for cancer therapy. NCI researchers have devised a cancer treatment strategy that kills cells containing B-cell or T-cell specific antigens. When this occurs the normal cells are regenerated, but the cancer cells are not. One strategy is to fuse the portions of antibodies that bind to CD22 (a B-cell antigen) or CD25 (a T-cell antigen) to a potent bacterial toxin termed Pseudomonas exotoxin A. The genetically modified toxin then specifically binds to and kills cells expressing CD22 or CD25. Since many lymphomas and leukemias express CD22 or CD25, these tumor cells are killed.

A promising ongoing NCI study is using this approach to combat B-cell malignancies. The antigen CD22 is expressed on about 70 % of lymphomas and leukemias. A recombinant immunotoxin termed BL22 has been designed and produced to kill tumor cells expressing CD22, and patients with hairy cell leukemia, chronic lymphocytic leukemia (CLL), and some lymphomas have been treated in a Phase I trial. Remarkable

anti-tumor activity has been observed in patients with hairy cell leukemia. Several patients with CLL have responded as well. Enrollment into this trial is continuing, and once the maximum tolerated dose is established, Phase II trials in hairy cell leukemia, CLL, and lymphomas (in a post-transplant setting) will be opened for enrollment.

Other antibodies under investigation are coupled to other potent anti-tumor substances, like radioactive molecules or anti-tumor antibiotics, and have the potential advantage of being able to deliver this tumor killing substance directly to the tumor site, where they attack antigen-positive tumor cells that other therapeutic agents might not penetrate well.

Anti-cancer vaccines are a high priority research area for NCI. Unlike conventional vaccines, which are used to prevent illness, the anti-cancer vaccines represent a therapeutic approach, which seeks to strengthen the body's natural defenses against diseases, such as cancer, that have already developed. Vaccine therapy for lymphomas has shown considerable promise. Results of a recently completed lymphoma vaccine study conducted by NCI researchers have shown that there is a clear anti-tumor effect in a small group of patients who were vaccinated over the course of five years. On the basis of these promising results, NCI has launched a large-scale, multi-institutional, randomized, phase III clinical trial, to definitively test the experimental vaccine, which is custom-made from patients' own tumors.

Immunotherapeutic approaches for treatment of multiple myeloma are also being evaluated. Investigators are examining the potential for immunization strategies in which a normal donor is vaccinated with the myeloma protein. The normal donor forms antibodies, called idiotype antibodies, and these are used to treat the patient. Preclinical studies of idiotype immunization demonstrate that this approach can induce an immune response that prevents tumor relapse or progression in myeloma models. Additional studies are determining the feasibility of inducing an active immune response against myeloma-specific antigens, such as MUC-1 and DF3.

The NCI is involved in the development of a large number of new therapeutic agents with a wide array of unique mechanisms of action. We now know that cancer arises from the disruption of fundamental cell processes. Basic research findings have identified a plethora of potential therapeutic targets for further exploitation. There is an ever-lengthening list of promising agents that affect cell cycle regulation, gene expression, apoptosis (programmed cell death), and other cell functions, currently undergoing or awaiting investigation in clinical trials.

A striking example of the benefit of this kind of molecularly targeted therapy is all-trans retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia (APL). ATRA works essentially by reversing the effects of a specific chromosomal translocation that disables both differentiation and apoptotic processes in affected cells. The introduction of this agent has increased the cure rate for APL from 40 percent to over 70 percent in just 10 years. Some patients who have been treated successfully with ATRA experience relapse, and recently, arsenicals, a group of rediscovered compounds that induce apoptosis via a different, more broadly applicable mechanism, have shown great utility as

a second line of defense against APL. Arsenic trioxide is now being evaluated for use in a variety of lymphoid malignancies, as well as other cancers, and for use in childhood APL, and also for use as a first line treatment.

Finding effective treatments for multiple myeloma has proven extremely challenging for cancer researchers. Recently, the success of thalidomide in treating MM patients has been very encouraging. Thalidomide effectively arrests tumor growth by stimulating anti-tumor immune response, interfering with communication between tumor cells and the surrounding tissue, and inhibiting the growth of new blood vessels (angiogenesis) near the tumor. Thalidomide's anti-angiogenic activity, was first recognized as the feature that caused birth defects in the children of women who took thalidomide in the 1950's and 1960's. Astute researchers theorized that the same feature could prove useful in restricting the blood supply to tumors. NCI-sponsored investigators recently report a 30 percent response rate for MM patients receiving thalidomide on a clinical trial. New trials are seeking to optimize the role of this agent, and some other antiangiogenic agents are being evaluated, as well. Because anti-angiogenic drugs have the potential to cause defects in a developing fetus, pregnant women are excluded from participating in clinical research on these drugs.

Bone marrow transplantation and peripheral blood stem cell transplantation techniques continue to be tested in clinical trials for certain LLM patients. Sometimes cancers become resistant to treatment with radiation therapy or chemotherapy. Very high doses of chemotherapy may then be used to treat the cancer. Because the high doses of chemotherapy can destroy the bone marrow, marrow is taken from the bones before treatment. The marrow is then frozen, and the patient is given high-dose chemotherapy with or without radiation therapy to treat the cancer. The marrow is then thawed and given back to the patient to replace the marrow that was destroyed. This type of transplant is called an autologous transplant. If the marrow is taken from another person, the transplant is called an allogeneic transplant. Another type of autologous transplant is called a peripheral blood stem cell transplant. The patient's circulating stem cells are collected, treated with drugs to kill any cancer cells, then frozen until they are returned to the patient. This procedure may be done alone or with an autologous bone marrow transplant.

The role of stem cell transplantation in caring for patients with LLM varies with tumor type. Autologous stem cell transplantation clearly benefits patients in a chemotherapy-sensitive relapse of their disease, but its role as initial treatment is undefined. A national trial is comparing the efficacy of initial transplantation with transplantation at the time of first relapse. Other studies are evaluating the role of biological therapies such as interleukin-2, and immune response stimulator, and rituximab for their effectiveness in enhancing the benefit of transplantation.

Many patients do not benefit from stem cell transplantation, and major efforts are directed at identifying the reasons and to develop methods to improve on these results. Some investigators are developing methods to harness patients' own immune responses. Alternatively, other researchers are using a technique called donor leukocyte infusion

(DLI) that introduces T cells capable of generating a graft-versus-tumor effect (in which the donor cells attack the patient's cancerous cells). However, they are also capable of generating a potent graft-versus-host disease (GVHD, in which the donor cells attack the healthy tissues of the patient) that could be fatal to the patient. Studies of the array of T cells that are present post DLI are being conducted to better understand which T cell populations are necessary to achieve the desired result while minimizing GVHD.

Allogeneic bone marrow transplant may cure patients who do not respond to standard chemotherapy, but the mortality of this procedure in patients with LLM has been very high. Moreover, age restrictions limit the number of patients who might be eligible for this procedure. There has now been an expanded information base on the use, for non-Hodgkin's lymphoma, of non-myeloablative transplants (in which the bone marrow is not completely destroyed) with DLI. Recently, investigators have described their experience with patients over the age of 55 years. GVHD occurred less frequently than expected and many patients were able to go through the procedure without requiring hospitalization. As a consequence, the notion that more intensive treatment is better is being challenged, and the role of the immune system in cancer progression is being better delineated.

The NCI sponsors the International Bone Marrow Transplant Registry, which is the world's largest body of data on outcomes following transplantation for LLM and other cancers. Data are provided from more than 400 centers and there are now data for more than 65,000 transplants worldwide. The information collected is used for determining transplant regimens for specific clinical situations, identifying prognostic factors, comparing transplant regimens, comparing transplant with non-transplant approaches, evaluating cost and cost-effectiveness, planning clinical trials, and developing approaches to evaluate outcomes.

Clinical trials for LLM treatment have demonstrated remarkable success and are a vital component of the NCI's research program. Currently, our clinical trials database contains descriptions of 177 NCI-sponsored leukemia treatment trials, 170 for lymphoma, and 67 for multiple myeloma. Our clinical trials program is the place where promising new strategies discovered at the laboratory bench are applied to real human problems at the bedside. Clinical trials offer cancer patients access to state-of-the-art care, and provide us the opportunity to learn something from every patient that may help someone else. Our rapid pace of discovery in the basic biology of cancer is refining our knowledge of how to intervene in cancer development, and clinical trials are the crucial final step in bringing these discoveries to people who are battling cancer.

Conclusion

Progress in our understanding of cancer and our ability to detect and treat it have led to a real and continuing decline in the cancer incidence and death rates. However, our excitement over important scientific progress and the very real human gains that result is tempered by the knowledge that far too many Americans continue to suffer and die from cancer each day. Moreover, all groups of people are not benefiting equally from our advances against cancer. NCI is embracing the challenge of understanding the causes of

health disparities in cancer and developing effective interventions to reduce them. Plans call for increasing fundamental research into the social causes of health disparities, the psychosocial factors that mediate them, and the biologic pathways that can explain their impact. In addition, we will expand our cancer control intervention and population research on disparities, better define and monitor cancer-related health disparities, and strengthen training and education in this research area. Effective communication empowers people to make informed cancer-related decisions and to engage in behaviors that will improve their health. Few other initiatives have the potential to simultaneously improve health outcomes, decrease health care costs, and enhance community satisfaction. Our intent is to learn how to help people distinguish important from insignificant health risks and deal with contradictory or inaccurate health messages so they can make informed choices.

Too many Americans, for a host of reasons, lack access to high quality, cutting-edge cancer treatment and care. NCI is launching research to improve the quality of cancer care by strengthening the information base for cancer care decision making. Researchers seek to better understand what constitutes quality cancer care, with an emphasis on the patient's perspective; identify geographic, racial/ ethnic, and other disparities in who receives quality care; and strengthen the scientific basis for selecting appropriate interventions. Our goal is to enhance the state of the science for defining, monitoring, and improving the quality of cancer care and inform Federal decision making on cancer care delivery, coverage, and regulation.

We have learned the value of including as broad a constituency as possible in our review, advisory, and planning activities, and we have forged new relationships with patients, practitioners, scientists in different fields of research and medicine, other government agencies, private sector companies, innovators in technology, and many other partners where such alliances were rare or non-existent only a few years ago. Illustrating our commitment to this philosophy as we seek to accelerate progress against LLM, the NCI convened a Progress Review Group (PRG) last year to conduct an intensive review of our research portfolio in LLM. This initiative, one of a highly beneficial series of PRG's fitting within NCI's new disease-specific planning framework, featured expert panels who provided a comprehensive view of the state of our current knowledge, and you will see that many of our research priorities will reflect the recommendations the PRG described in their report, issued last month, and available on our website at: <http://prg.nci.nih.gov/llm/finalreport.html>.

We have a special interest in enlisting the help of cancer survivors. The NCI created the Consumer Advocates in Research and Related Activities (CARRA) program to encourage people affected by cancer to provide their viewpoint and ideas directly to NCI staff so that the NCI can incorporate this perspective into our programs and activities. Our goal is to recruit 150 consumer advocates (cancer survivors, family members, or those who are involved in cancer-related activities like support groups, cancer hot lines, or advocacy groups) to become members of CARRA and represent many different cancer types, age groups, and ethnic groups from across the Nation. In addition to participating in NCI activities, CARRA members will represent the opinions of their groups and play

critical roles as two-way information links between their own communities and constituencies and the NCI.

NCI has been entrusted with guiding our Nation's commitment to a complete understanding of cancer: from understanding how a normal cell becomes cancerous to understanding why some people get cancer and others do not; and across the continuum through detection, diagnosis, treatment, survivorship, and ultimately prevention. NCI's mission is broad and our approach is necessarily ambitious, because, while our primary role and our expertise is research, our interest is people: our families, friends, neighbors, and colleagues - and yours. Our goal is to eradicate cancer and save the lives of those who would otherwise be lost to us.

Thank you, Mr. Chairman, for giving me this opportunity to share with you our progress against hematologic cancers. I will be pleased to answer any questions you may have.