

"Cancer Treatments for the 21st Century"

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Opening Statement

Good afternoon. It is always a pleasure to speak with you about the progress we are making in cancer research, and to discuss the importance of public understanding of these advances.

I can say unequivocally that we are making real progress against cancer. We measure progress against cancer in two ways: first, the increase in knowledge about cancer, and second, the reduction of the burden of this disease on people. I will tell you about progress in both our fundamental understanding of this disease and in our efforts to prevent and treat it. But first I want to say that progress made in both areas is already evident in the declining cancer incidence and death rates. Between 1990 and 1995, these rates dropped for all cancers combined and for most of the top 10 cancer sites, reversing an almost 20-year trend of increasing cancer cases and deaths in the United States.

After increasing 1.2 percent per year from 1973 to 1990, the incidence rate for all cancers combined declined an average of nearly 1 percent per year between 1990 and 1995. The rates declined for most age groups, for both men and women, and for most racial and ethnic groups. The exceptions were black males, where the rates continued to increase, and Asian and Pacific Islander females, where the rates were level. The overall death rate declined an average of 0.5 percent a year from 1990 to 1995, with the declines greater for men than for women. The only racial and ethnic group not included in the downturn was Asian and Pacific Islander females.

These decreases are good evidence of the power of this Nation's investment in cancer research and of the value of carefully conducted basic research and clinical trials. We also realize that these declines, while encouraging, must be accelerated and extended so that all of our population benefits.

Recent Advances in Understanding Cancer

As we understand the nature of cancer, we understand that it is a unique set of diseases, and that the answers to cancer are related to the most fundamental mysteries of life itself. We know that cancer is not one disease, but at least 100 different diseases that share

certain features. Because of this it is unlikely that one magic bullet will solve the problem.

The most remarkable progress in the past 25 years has been in our knowledge of cancer biology. We are dramatically extending our understanding of what is required to turn a normal cell into a cancer cell. Cancer arises when a single cell changes so that it divides continuously, released from the controls that constrain the replication of normal cells. This transformation results from changes in the function and activity of genes. Of the approximately 100,000 genes found in the human genome, the altered activities of only a relatively small number of genes are responsible for transforming a normal, well-behaved cell into a cancer cell. Identifying these cancer genes defines the central scientific hunt in cancer biology, and opens an unprecedented window into the nature of cancer. Up until now, our detection tools have lacked the sensitivity and the specificity that we must demand if early detection is to be useful and successful. Our interventions, despite their success, have, by and large, been the result of guesswork. But now, we are at a point where we can transform our approach to cancer.

No one genetic alteration is enough to make a normal, healthy cell a cancer cell. Rather, an accumulation of changes in a relatively small number of genes during the lifetime of a cell is required. We have learned that some individuals carry a very high lifetime risk of developing cancer. This understanding has allowed us to begin describing the evolution of specific cancers from predisposition to pre-cancer to cancer. Each cancer is ultimately defined by its particular pattern of altered and normal gene activity. This unique pattern determines the cancer's rate of growth, tendency to spread, responsiveness to hormones and therapies, and also predicts the ability of a person's immune system to recognize and respond to the cancer. Moreover, cataloging these molecular patterns will ultimately tell us how many different cancer exist, and enable us to distinguish the differences between a cancer cell and a normal cell.

We also are learning to understand the causes of cancer. Research on cancer risk — the probability that the disease will occur in a given population — is identifying populations with a significant probability of developing cancer. Because cancer is a multistage process, analysis of risk factors leads to the development of prevention and control strategies, as well as early detection methods, and in some cases more precise treatments. Epidemiologic research has identified many factors that increase cancer risk. Most of these are related to environment and lifestyle, while others are part of a person's genetic makeup. With the exception of a few genetic conditions, however, it is still not possible to predict with any degree of certainty that a person having one or more of these factors will develop cancer. This uncertainty is related to the very nature of cancer and the need for many specific alterations to accumulate in a single cell for that normal cell to be transformed into a cancer cell.

Advances in Therapy

Forty years ago, it was not clear that cancer, other than that which could be removed surgically, could even theoretically be cured. The first proof that cancer can be treated

and cured came with childhood cancers, where survival was once measured in weeks to months and where now the great majority of children with cancer are cured. Now, for some cancers, our ability to cure is relatively predictable. For others, our ability to cure is remarkably unpredictable.

The National Cancer Institute is committed to improving cancer treatment through research that will develop novel new approaches and improve the effectiveness and reduce the side effects of standard treatments. Advances in therapy are coming in three approaches. First, we are learning to tailor treatments for a specific cancer in a specific individual. Second, we are optimizing the results of traditional treatments. Third, we are learning to target treatments to the nature of specific tumors.

Tailoring cancer treatments to a specific cancer in a specific individual depends on the ability to precisely describe a given cancer. Better diagnostic tools could allow us to determine the behavior of each cancer — how it responds to therapy, how it changes over time, and whether it threatens the patient.

Just as each person's signature and fingerprints are distinct from those of every other person, cells likewise have signatures — unique, identifiable characteristics related to their role in the body. During the transformation of a normal cell into a cancer cell, the signature changes, and that change becomes a unique signal of that cancer cell's presence and character. The more that is known about a particular tumor, the easier it is to make correct choices about therapy and accurate predictions of outcome. For example, some breast cancer cells produce a protein called HER2 or HER2/neu. When that protein is detected, treatment can be tailored to those cancer cells. In another example, some breast tumors express estrogen receptors, which can positively affect prognosis. Knowledge of the presence of a particular receptor can help the physician to tailor treatment most effectively.

Cancer research is also improving the traditional mainstays of treatment — surgery, radiation, and chemotherapy. Clinical trials are instrumental in these improvements. As examples, within the last two years we have established new standards of optimal therapy for women with node-negative and locally advanced breast cancer, for women with advanced ovarian cancer, for melanoma, and for childhood renal cancer. These new approaches to cancer therapy are the direct result of the Nation's clinical trials system.

Early findings of a large, NCI multi-center trial, show that the drug Taxol, when used in combination with other standard chemotherapy agents, has a small but significant benefit for breast cancer patients whose disease has spread to nearby lymph nodes. Although the survival advantage is small at this point in the trial, the study is considered important because it is the first to show that Taxol may be beneficial in the initial, post-surgical treatment of some women with localized, node positive breast cancer.

Longer follow-up of this trial and results from other confirmatory trials are needed before the addition of Taxol or similar drugs becomes routine. Other trials now under way will provide much needed data on the optimal, adjuvant treatment for node positive breast

cancer patients. One trial should finish recruiting patients soon. Early findings could be available in the next one to two years. Another trial using Taxotere, a drug similar to Taxol, in the treatment of node positive breast cancer is still open to new patients.

In addition, improvements in traditional treatments are likely with the addition of agents that can improve the effectiveness of the standard modalities. For example, Gadolinium Texaphyrin is an agent that appears to sensitize cells to the killing effects of both radiation and chemotherapy. It is absorbed by tumors to a much greater extent than by healthy tissue and, therefore, makes the tumor more susceptible to killing. Use of this compound holds particular promise for treating brain tumors. Finally, research is underway to develop analogues of effective drugs to reduce toxicity, while maintaining effectiveness.

With the third approach — targeting treatment to the nature of the tumor — recent developments in understanding the basic machinery of cancer resulted in development of more refined techniques that target cancer at the molecular level. It is at this level that we hope to interrupt the development of tumors, and potentially eliminate cancer. As part of this approach, efforts are under way to improve immunotherapy through the use of monoclonal antibodies and vaccines.

The first monoclonal antibody to be approved by the Food and Drug Administration for use as a cancer treatment is a monoclonal antibody that targets CD20, a protein found on the surface of B-cell lymphocytes. It was developed by NCI and industry and shows effectiveness in treating relapsed, low-grade lymphomas. Another monoclonal antibody to CD20, but with a radioactive isotope attached, is being tested in clinical trials and also shows some promise against low-grade lymphomas.

Another monoclonal antibody showing promise for cancer treatment is Herceptin. Developed by a biotechnology company, Herceptin is one of a specific group of drugs designed to attack specific cancer cells — cells that produce a protein called HER2 or HER2/neu, which occurs in high numbers in about 25 percent to 30 percent of breast cancers. Favorable study results indicate that Herceptin may be beneficial for some patients with breast cancer that produces HER2/neu and has spread to other parts of the body. Unlike chemotherapy, Herceptin leaves healthy cells alone. However, few treatments are without side effects and Herceptin is no exception. It can cause heart problems, although these have been shown to be treatable in patients who manifest these symptoms.

NCI is supporting two major studies with Herceptin through NCI-sponsored cooperative clinical trial groups. One is a phase I pilot study of low dose interleukin-2 plus Herceptin in a variety of solid tumors. The second is a Phase II study of Herceptin in recurrent or refractory ovarian or primary peritoneal carcinoma. Current supplies of Herceptin are extremely limited. While awaiting FDA review, Genentech is increasing production and continuing to expand access. However, until a larger supply is available, Genentech is making the drug available through a lottery system. Additional studies are planned to test Herceptin in combination with other agents.

Vaccine development is another major area of research designed to elicit a targeted immune response in patients against their tumor cells. Researchers at NCI have designed a synthetic vaccine to be used to evoke an immune response in patients with melanoma, an often-deadly form of skin cancer. This vaccine is comprised of a peptide that mimics the antigen that sits on the surface of a patient's own tumor cells. Results of early clinical trials involving 31 patients whose melanomas had spread to other sites in the body demonstrate that it is possible to get the immune system to respond even when patients have a heavy tumor burden.

Another example of targeted treatment, anti-angiogenesis research, has been highly publicized recently. In normal tissue, new blood vessels are formed during tissue growth and repair, and the development of the fetus during pregnancy. In cancerous tissue, tumors cannot grow or spread without the development of new blood vessels that supply the cancer with oxygen and nutrients needed for survival and growth. About 20 angiogenesis inhibitors, intended to block the development of new blood vessels that feed a tumor, are now being tested in human trials, and others that have shown success in animal trials (including angiostatin and endostatin, the two that received much publicity) will enter human trials when supplies are available.

Angiogenesis is also related to metastasis. It is generally true that tumors with higher densities of blood vessels are more likely to spread and are correlated with poorer clinical outcomes. Angiogenesis inhibitors target dividing endothelial cells rather than tumor cells. Consequently, it is hoped that they will not cause bone marrow suppression, gastrointestinal symptoms, or hair loss, all symptoms associated with standard chemotherapy treatments. Thus far, research in animals has not found any problems with development of drug resistance, another problem faced by standard chemotherapy. Anti-angiogenic therapy may prove useful in combination with therapy directly aimed at tumor cells. Because each therapy is aimed at a different cellular target, the hope is that the combination will prove more effective.

Scientists at a biotechnology company developed a genetically engineered adenovirus that is unable to invade healthy cells, but can invade cancer cells that have a flawed version of p53. This flawed gene is implicated in an estimated 50 percent of human tumors. At a recent meeting, a company scientist reported that two of 10 patients with head and neck cancer who were infected with the virus, in addition to standard chemotherapy, had complete disappearance of their tumors and seven had reductions in tumor size of more than 50 percent, with some reductions as much as 95 percent. Although this development is promising, it is too early to tell if the responses will last.

Still another targeted treatment approach is photodynamic therapy, the use of lasers and light-activated drugs to kill tumors. In January, the Food and Drug Administration approved the use of Photofrin, a light-activated drug, for use in photodynamic therapy for patients with microinvasive lung cancer who are not eligible for surgery or radiotherapy. The drug had received approval earlier for palliative treatment of certain cancers, but this was the first North American approval of the therapy for a potentially curative use. It was previously approved in Japan and Germany for early stage lung cancer treatment.

Cancer Prevention

Efforts at cancer prevention have long focused on preventable causes. A major target has been tobacco use, the most important exposure increasing cancer risk. Other targets have included diets high in fats and low in fiber, alcohol consumption, radiation, sunlight, occupational exposures (such as asbestos), environmental pollution, pharmaceutical agents (such as estrogenic drugs), and viruses (such as the human papilloma virus).

Now, our concept of prevention is expanding based on the new knowledge of the nature of cancer and how it develops. This knowledge led to an approach called chemoprevention, the use of agents as cancer preventives. More than 50 other compounds are under study as potential cancer preventive agents.

This year, the Breast Cancer Prevention Trial, a study of the use of tamoxifen as a breast cancer prevention agent, was unblinded 18 months early because the drug was overwhelmingly successful in preventing breast cancer in women at high risk of the disease. Tamoxifen reduced breast cancer incidence 45 percent in high risk women.

Women taking tamoxifen also had fewer bone fractures of the hip, wrist and spine (47 cases versus 71 cases in the placebo group). However, it was also revealed that tamoxifen increased a woman's chances of developing three rare, life-threatening health problems: endometrial cancer, pulmonary embolism, and deep vein thrombosis. Among the women taking tamoxifen there were 33 cases of endometrial cancer versus 14 cases in the placebo group, 17 cases of pulmonary embolism versus 6 cases in the placebo group, and 30 cases of deep vein thrombosis versus 19 cases in the placebo group. Thus, even if a woman is at an increased risk of breast cancer, the decision to take tamoxifen must be made after considering both the risks and benefits of this therapy.

Raloxifene has recently been publicized as a drug which shows promise in the prevention of breast cancer. Recently, FDA approved raloxifene for the treatment of osteoporosis, and data from clinical trials also showed a reduction in the numbers of breast cancers diagnosed in the treatment group. However, little is known about the effectiveness and potential side effects of raloxifene. Last month the NCI-supported National Surgical Adjuvant Breast and Bowel Project (NSABP) announced its intention to conduct a new large-scale breast cancer prevention trial to compare the effectiveness of tamoxifen and raloxifene. Approximately 200 clinical centers across North America will participate. This chemoprevention clinical trial will compare the efficacy of five years of tamoxifen therapy to five years of raloxifene therapy in preventing invasive breast cancer. Up to 22,000 postmenopausal women over the age of 35 will participate. The study is scheduled to begin this Fall.

Prostaglandins, fatty acids that affect cell function in every organ system, are produced in cells lining the joints where inflammation and proliferation take place in rheumatoid arthritis and osteoarthritis. These prostaglandins also appear to be important in cancer development because they affect cell division, cellular adhesion, immune surveillance, and apoptosis. The prostaglandins are synthesized by two different forms of

cyclooxygenase, enzymes designated as COX-1 and COX-2. The enzymes are found in tumor tissue, particularly colon tumors. COX-2 is particularly active, leading to increased prostaglandin production in transformed cells and tumors. Over-expression of COX-2 increased invasiveness and resistance to cell death.

Researchers at several drug companies have developed compounds that selectively inhibit COX-2, and two of these compounds are in late stages of clinical testing. Some studies in animals have shown that COX-2 inhibitors reduced the formation of intestinal tumors in rats and mice by 87 percent. Two chemoprevention trials with the inhibitors are being planned. One will look at regression in familial polyposis; the other will look at the drug's effects on biomarkers and development of adenoma in patients with non-hereditary polyposis.

NCI is actively pursuing development of a vaccine to prevent cervical cancer. This vaccine is based on the concept that almost all cervical cancers are caused, at least in part, by papilloma virus infections. The vaccine is likely to be safe since it is not infectious and does not contain the potentially cancer causing viral genes. Clinical grade vaccine is in the final stages of preclinical evaluation and early phase trials will be conducted by the NCI intramural program in collaboration with NIAID and Johns Hopkins University.

NCI also conducts and supports research into behavioral aspects of cancer prevention, such as smoking cessation, dietary interventions, and risk communications.

Public Understanding

Communicating with cancer patients, individuals at high risk for cancer, the general public, and the health care community is a central component of NCI's mission and mandate. Our programs are based upon needs identified through epidemiologic studies and market research among specific population groups, resulting in programs that are relevant and understandable to each group. Our patient education program, leadership initiatives for special populations, and minority research networks are all actively involved in spreading state-of-the-art information about cancer prevention, detection, diagnosis, treatment, and care.

The primary avenues NCI uses to communicate with the public and the health care community are:

World Wide Web (<http://www.nci.nih.gov>): Currently NCI is redesigning its web site to increase its usefulness as a communication tool. The new web site will be organized so that clinicians, researchers, and the public can quickly and easily locate up to the minute information that is relevant to their needs. A new addition to NCI's Web site is the cancerTrials site (<http://www.cancertrials.nci.gov>). Through this site, patients, health care professionals, and the public can learn about ongoing NCI-sponsored trials, read about the most recent advances in cancer therapy, and explore other information resources related to cancer treatment. This web site was used by many patients and others who wanted information about treatment advances publicized over the past several months.

Cancer Information Service: The CIS provides accurate, up to date cancer information to patients and their families, the public, and health care professionals in every state through 19 offices located at NCI-funded Cancer Centers and other health care institutions. By dialing 1-800-4-CANCER, callers are automatically connected, free of charge, to the office serving their region. Information on specific cancer types, state-of-the-art care, clinical trials, and resources such as support groups or screening and smoking cessation programs is provided in English or Spanish by specialists who respond to more than 600,000 inquiries annually. The CIS regional offices are NCI's focal point for state and local cancer education efforts that target underserved, high risk, and low literacy populations. Thousands of patients and others called the CIS to get more information about recent treatment advances that were in the news. The system is experiencing a higher busy signal rate that NCI wishes and efforts are being made to address that problem.

Physician Data Query (PDQ): Patients and health care professionals want and need access to accurate, up to date, comprehensive information about ongoing clinical trials. Through PDQ, NCI provides information about NCI-sponsored trials. We are in the process of expanding the database, with the cooperation of patient advocates, the Food and Drug Administration, and the pharmaceutical industry, to include all cancer clinical trials approved by the FDA and to revamp the way information is presented. This system has served as a model for other institutes at the National Institutes of Health, and we want to ensure that it continues to be responsive to the needs of the communities we serve.

Medical choices are increasingly made on an individual basis, requiring that physicians and their patients have access to the resources needed to make an informed decision about their treatment and care.

Communicating the importance of research findings to physicians and patients in a clear and understandable manner is central to making critical decisions about a patient's treatment and care. We must be ready to give complete and balanced information. We are in the process of developing such tools for tamoxifen to supplement the information that has already been widely reported publicly. For example, last week the NCI sponsored a workshop of national experts to develop ways for health professionals and women to decide whether a woman is a candidate for using tamoxifen as a preventive agent. As part of this effort, NCI is creating a computer disc to help physicians to determine a patient's risk of breast cancer and will distribute the disc widely.

NCI is committed to improving public understanding of emerging science and will continue to work with its public and private partners to raise public awareness of key issues in the treatment and prevention of cancer.

NCI will work with its partners to provide the public with accurate, useful, and timely information for physicians, cancer patients and their families. We all recognize the potential for a scientist's enthusiasm and excitement to be captured in a sound bite that can easily be misinterpreted out of context, and we need to try very hard to avoid such situations.

I will be happy to answer any questions.