Susan B. Komen Foundation 2000 Conference

By Robert H. Carlson

Breast Cancer: Setting Priorities for Moving toward Long-Term Management

WASHINGTON, DC—A sense of urgency is a driving force within the Susan G. Komen Foundation says founder and chair Nancy Brinker. She illustrated this in a question she put to panelists during a session here at the recent Susan G. Komen Breast Cancer Foundation 4th Annual National Grant Conference, “Reaching for the Cure, Making a Difference.” She asked, “If you had to characterize three priorities that would quickly move us closer to long-term management of breast cancer—rather than prevention or cure—what would they be?”

Application of Existing Treatments

Nancy E. Davidson, MD, Director of the Breast Cancer Program at Johns Hopkins Oncology Center in Baltimore, emphasized practical application of existing treatments over new breakthroughs when thinking of long-term survival.

“If you had to characterize three priorities that would quickly move us closer to long-term management of breast cancer—rather than prevention or cure—what would they be?”

“While the emphasis at this meeting is on research, I believe we should take what we already know and apply it to patients today in widespread clinical practice,” she said. Public education about detection was Dr. Davidson’s second recommendation, followed by increased efforts to reduce the toxicities of current therapies.

Gabriel Hortobagyi, MD, Chairman of the Department of Breast and Gynecologic Medical Oncology at MD Anderson Cancer Center in Houston, said that it is critical to accelerate translational research from the laboratory to the clinic. “But I would venture to say that what we know today, without even waiting for the research tomorrow, we could be saving tens of thousands, perhaps hundreds of thousands, of lives, by emphasizing what our strengths are now, if we could break down the barriers to optimal screening with mammography, to the optimal use of breast-conserving surgery and adjuvant systemic therapy,” he said.

Dr. Hortobagyi said that screening alone is known to decrease mortality by at least one third, and he cited a number of projects in imaging and in the development of markers that he called very exciting. “These should be high-priority projects because they carry relatively little risk or toxic effects, and, under the best of circumstances, they could have very positive effects on early diagnosis,” he said.

Development of a breast cancer treatment targeting the galactosyl transferase gene is about two years away from clinical trial, according to Charles Link Jr., MD, Director of the Human Gene Therapy Research Institute at the John Studdard Cancer Center at Iowa Methodist Medical Center. Resistance can stay in chemotherapy, often fail to control the primary tumor, and may ultimately fail to control the different components—at only how much benefit chemotherapy or tamoxifen has,” he said as an example. “When you look at the combined beneﬁts [of early treatment], there is a substantially greater advantage than we think, and we need to build on that.”

Dr. Hortobagyi’s second idea for improving long-term treatment was to concentrate on the emerging knowledge of the effects of interventions on individual genes. In recent decades it would have taken a young researcher five or 10 years of a career to work with one gene and understand what it does, and perhaps only to dream of modifying that gene, he noted.

“The third panelist, Clifford Hudis, MD, Chief of the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center in New York City, agreed with Dr. Davidson that lack of public education remains a major impediment to screening and to treatment. He also agreed that simply by applying what is already known about breast cancer management and making it accessible to women in a consistent way, regardless of their needs and socioeconomic status, could tremendously improve outcome.”

It remains an embarrassment, in a sense, that different socioeconomic groups have differing outcomes to cancer when there is little reason to believe that biologically the disease is any different,” he said.

Dr. Hudis concluded by calling for broader participation in clinical trials. “In spite of an amazing growth of knowledge about the biology of breast cancer, and in spite of dozens and even hundreds of new compounds poised to be tested, participation in clinical trials among adult Americans is disappointing,” he said. This is in contrast with the situation in pediatrics in which the majority of children are treated on research studies.

“It is frustrating for all of us to see patients decline trials in order to get what they consider the best therapy, because we know there is so much more to be done,” he said. “Education of the public about the potential gains and values of clinical trials, about the wisdom of participating in trials, and the elimination of external barriers to enrollment such as reimbursement issues, could all do much to improve outcomes in breast cancer.”

Roundup of Promising Breast Cancer Basic Research

WASHINGTON, DC—The first two Susan G. Komen Foundation grants, in 1983, were for $15,000 each. The foundation now is the largest private funding source for breast cancer research and community outreach programs in the United States, awarding more than $44 million in grants in 1999.

Scientist recipients of current foundation grants were invited to the recent Susan B. Komen Foundation 2000 Conference here, to describe their ongoing research. Founding Chair Nancy Brinker said the goal of these sessions was to showcase cutting-edge research, with an emphasis on discussing how the information can be translated to have the greatest impact at the community level. The following are some of the highlights.

Development of a breast cancer treatment targeting the galactosyl transferase gene is about two years away from clinical trial, according to Charles Link Jr., MD, Director of the Human Gene Therapy Research Institute at the John Studdard Cancer Center at Iowa Methodist Medical Center. The goal of the research is to convert breast cancer cells into a vaccine as a way of increasing immunity. Dr. Link explained. “Despite many abnormal genes produced within the breast cancer cell, the body does not reject the cell, and we are trying to reverse that.”

The researchers have inserted a murine alpha 1,3-galactosyltransferase gene into human breast cancer cells, with the intent of making the breast cancer cells appear to the immune system as if they were transplanted from a mouse. Galactosyltransferase is a sugar molecule that appears in lower mammary glands but not in humans and is often responsible for xenograft hyperacute rejection that often prevents use of mouse-derived vaccines in humans.

Doxorubicin and daunorubicin, mainstays in chemotherapy, often fail to eradicate cancer because of systemic toxicities and cellular resistance, noted Leonard Lichtenstein, PhD, Associate Professor in the Department of Pharmacology at the University of Tennessee Health Science Center. Resistance can be due to the presence of cancer cells.

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Breast Cancer Research Directions Reviewed

WASHINGT0N, DC—It is a challenge for medical researchers to address an audience of community volunteers, patient advocates, laboratory scientists, and oncology clinicians, keeping them all awake and attentive. Such was the case here at the recent Susan B. Komen Foundation 2000 Conference where several of the speakers proved they were up to the task, reviewing recent advances in breast cancer research and treatment for a diverse mix of attendees.

In a plenary session, Nancy E. Davidson, MD, Director of the Breast Cancer Program at Johns Hopkins Oncology Center in Baltimore, described investigations into “new ways to use old drugs, fine-tuning their utility” through dose intensification or sequencing. She discussed sequencing trials of doxorubicin and taxanes, which have yielded improvements in outcomes. She added that as for dose intensification, she said the jury is still out on trials of high-dose chemotherapy with stem cell transplantation.

Three biological therapies that Dr. Davidson said she considers on the forefront are Herceptin and recombiant MAB-VEGF, both being tried in combination with paclitaxel, and the angiogenesis drug marimastat, now in a placebo-controlled trial of women with metastatic breast cancer after relapse following taxane or anthracycline therapy.

Another plenary speaker, Mary-Claire King, PhD, Professor of Medicine and Genetics and Walt Disney-American Cancer Society Professor for Breast Cancer at the University of Washington in Seattle, reviewed her years of research on BRCA1 and -2 in breast and ovarian cancers, up to an ongoing project involving tamoxifen. She said her laboratory is sequencing the genes from blood samples of all the women who took part in the placebo-controlled National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, which showed reduction in the risk of breast cancer in high-risk women over age 35 who took tamoxifen. Outcomes will be matched to BRCA status when the sequencing portion of the project is done.

“When we simply count, and then we will know whether tamoxifen did lead to a reduction in incidence of breast cancer among women with BRCA-1 and -2 mutations,” she said. In another presentation, Clifford Hudis, MD, Chief of the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center in New York City, covered a wide range of clinical investigation, including attempts to predict outcome in women with ductal carcinoma in situ and derive prognoses from tumor size and nodal status.

Dr. Hudis also mentioned geldanamycin, a modified benzoquinoid ansamycin that he said “poisons HER-2 in breast cancer cells.” He noted that research of this nature is very different from drug-discovery studies in the 1960s and 1970s, when scientists would grow cancers in wells and test hundreds of drugs against cell lines—that “non-targeted empirical approach was the best we could do at the time,” he said.

Tests with geldanamycin are in the very early stages, he said. But even though the drug may prove to be a “non-starter,” he is excited that the research “represents a way in which our understanding of HER-2 and Herceptin has lead to something that is rational rather than just empiric.

“This is very different, and it is elegant research even if it doesn’t get us [to a viable treatment] tomorrow,” he said, crediting Drs. Neil Rosen and Pam Munster for much of the work being done on the drug at Sloan-Kettering.

In a workshop at the meeting, Joyce O’Shaughnessy, MD, Director of the Chemoprevention Research Program at US Oncology Research in Dallas, listed several questions that remain unanswered: the controversy around complete hormonal blockade after chemotherapy using ovarian suppression plus tamoxifen, the question of prophylactic bisphosphonates in women with localized breast cancer to prevent bone metastases, and doubts regarding use of high-dose chemotheraphy with stem cell rescue.

She promised that results from future trials will put a stop to “one size fits all” therapy. Women with breast cancer will see their treatments tailored by markers such as hormone receptors and HER-2 and p53 status, as well as practical considerations such as chemotherapy regimens that avoid alopecia. She also voiced a commitment to finding therapies with minimal toxicity: “We can’t be giving symptoms [from therapy] to women who don’t have symptoms from the cancer.”

Basic Research

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that are defective in their ability to trigger apoptosis in response to drug or radiation-induced cellular damage. These resistant cells often produce higher than normal levels of the proteins Bcl-2 or Bcl-X(L), both of which normally help prevent premature cell death.

Dr. LoBello described a new drug, AD198 (14-0 acyl anthracycline), that is structurally similar to doxorubicin but functionally distinct in that it is cytotoxic through rapid-triggering apoptosis rather than by simply causing cellular damage.

Bcl-2 expression does not inhibit AD198 activity, he reported. Also, unlike doxorubicin, AD198 does not enter the cell nucleus and does no direct damage to DNA, yet it is as cytotoxic as doxorubicin. In a mouse model AD198 is entirely noncardiotoxic, and the drug’s toxicity appears to be bone marrow suppression.

Dr. LoBello noted in his presentation that he has a special interest in this project, since he is the husband and son of breast cancer survivors.

Sensitizing Tumor Cells

The Herceptin receptor in breast cancer tumors is activated through dimerization by heregulin, producing a wide range of growth factors that promote cancer. This makes the heregulin molecule a typical candidate for use of rational biological drug design, said Ruth Lupu, PhD, Senior Scientist at Lawrence Berkeley National Laboratory.

Although heregulin induces tumor growth, it also sensitizes breast cancer cells to chemotherapy, she noted. The goal of her research is therefore to dissociate these different functions from each other.

Dr. Lupu and colleagues have developed a distinct modified heregulin molecule that retains its chemosen- sitization property while losing the tumor-promoter property. Using this product to sensitize tumor cells to doxorubicin or etoposide may lead to lower systemic cytotoxicity without sacrificing efficacy.

Class Action

The search for a microtubule stabilizing agent similar to paclitaxel but without its multidrug resistance problems has led researchers at Albert Einstein College of Medicine in New York City to epothilone B. This water-soluble discodermolide is a natural product recently isolated from myxobacterium spirochaetae by researchers at the University of Southern California Keck School of Medicine in Los Angeles.

Hayley M. McDaid, PhD, a postdoctoral fellow in the Department of Molecular Pharmacology, reported that epothilone B appears to share the same mechanism of action as paclitaxel, and that it may be synergistic with paclitaxel even though both are in the same drug class.

Using a mathematical model, she and her colleagues found that low doses of both drugs given in combination showed synergistic inhibition of tumor cell growth and enhanced tumor cell death in two breast cancer cell lines. “This observation is unusual because both drugs are in the same class, and our future efforts will focus on understand- ing how this synergy occurs and whether it can be translated into patient care,” she said. “The synergism could potentiate cell death at lower doses of paclitaxel.”

Dr. McDaid reported that a Phase I exploratory study with seven patients showed that the drug, given at a dose of 50 mg/m2, produced an effect within one hour. She gave no details on the drug’s toxicity, but said that Novartis is analyzing the preclinical data.

Engineered Protein

The aim of gene therapy is to develop “molecular missiles”—molecules that provide targeted delivery of therapeutics, said Lali K. Medina-Kauwe, PhD, Senior Researcher at the Institute for Genetic Medicine at the University of Southern California Keck School of Medicine in Los Angeles.

She described her gene-therapy research with penton, a surface protein that plays a significant role in the cellular internalization of adenovirus. The USC team has shown that an engineered penton protein called PKB-10 can seek out breast cancer cells, and it has now been further engineered to contain heregulin as a potential breast cancer vaccine.

Overcoming Paclitaxel Resistance

TLO3 is a synthesized taxane analog shown in in-vitro studies to be 500 times more active than paclitaxel or docetaxel in killing taxane-resistant human breast cancer cells as well as sensitive cells.

A new distinct modified heregulin molecule retains its chemosenstization property while losing the tumor-promoter property.

It has been developed to overcome paclitaxel resistance, but it is also less toxic to normal tissues, reported Li-Xi Yang, MD, PhD of California Pacific Medical Research Center in San Francisco. He said that in vitro studies show increased apoptosis and caspase-3 activity significantly correlated with the enhanced cytotoxicity of TLO3.