TRENDS-in-MEDICINE

BULLETIN:

AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) – PREVIEW

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by Lynne Peterson

For the first time, AACR held a web conference with reporters in advance of the annual meeting (April 15-18) in Chicago. AACR President Michael Caligiuri, MD, president/physician-in-chief at City of Hope National Medical Center, said the meeting has four themes: immunotherapy, precision medicine, disparities, and prevention, with 170 trials to be presented over 4 days. And he emphasized, repeatedly, that the focus at AACR is on the "pursuit of science."

The choice of Elaine Mardis, PhD, co-executive director of The Institute for Genomic Medicine at Nationwide Children's Hospital, as the program chair for the meeting emphasizes just how important genomics has become in cancer science. Dr. Mardis is a well known cancer genomics expert and for many years was one of the key organizers of the Advances in Genome Biology and Technology (AGBT) meeting. On the webcast 4 studies were highlighted.

CAR T – quality not just quantity matters

David Barrett, MD, PhD, a pediatric hematologist from Children's Hospital of Philadelphia (CHOP), reported on their finding that T cell dysfunction in pediatric cancers can limit the effectiveness of CAR T therapy. In exploring why the T cells harvested from some pediatric patients had really poor quality or didn't survive at all, the researchers found that chemotherapy can make the T cells less viable or expandable. There was also a difference in T cell viability by type of cancer, with T cells from acute lymphoblastic leukemia (ALL) and Wilms patients having cells well suited for CAR T, but lymphoma – and most solid tumors – have quite poor cells for T cell expansion.

The T cells that don't work, Dr. Barrett said, are "exhausted in some way, shape, or form – either by the tumor or the chemotherapy. And we can now predict who will do well and who won't."

Dr. Barrett said the findings have already changed practice at CHOP, "Based on these data we have altered our practice for T cell collection…We will collect T cells early, even if that patient is not currently eligible for a CAR T trial…and we are recommending that to other centers. Especially, in the case of leukemia, we have already altered practice to think ahead…For solid tumors, we are still churning through the data, and we will see if we can make a best recommendation then."

Asked if CAR T should be considered earlier instead of chemotherapy, Dr. Barrett said, "80%-90% of pediatric leukemia is cured with standard chemotherapy…so the bar to move CAR T forward is different than for metastatic osteosarcoma where long-term survival is <20% with standard chemotherapy and surgery. So, we have to look at the prognosis with each disease, but, certainly, if we want to do immunotherapy, we need to think of doing it earlier."

Asked what the implications of these findings are for other cancers and for adult patients, Dr. Barrett said, "What I hope translates to research and to adults is my colleagues really taking a much harder look at the quality of the T cells we are getting…and can we use these findings to do adaptive manufacturing…and make it even more personalized, tailored to whatever problems we find in a

particular patient…I hope this will help us look at the problem beyond just the number [of T cells]. At first it was just how many T cells you got, and now we know there are differences in the quality."

Precision medicine – Puma Biotechnology's Nerlynx (neratinib)

ER+ metastatic breast cancer is the most common cause of breast cancer mortality in the U.S., with more than 20,000 deaths/year. While aromatase inhibitors, tamoxifen, and SERMs are the mainstay of treating these patients, Utthara Nayar, PhD, a researcher from Dana-Farber Cancer Institute, said that virtually all of these patients develop treatment resistance. Her study found that ER mutations, found in 25%-30% of ER+ metastatic breast cancer patients, confer resistance to aromatase inhibitors, and that activating HER2 mutations are a distinct mechanism of action of this resistance. She also reported that HER2-activated mutations can be overcome with neratinib, an irreversible HER2 inhibitor but not by reversible HER2 inhibitors, in combination with fulvestrant.

Dr. Mardis said the importance of this study was (a) how next-generation sequencing (NGS) was able to look at pre- and post-development of resistance and (b) how it plays into liquid biopsies, "It is often difficult to get metastatic tumors to study, but if we know what to look for, we can monitor by liquid biopsy…and that may let us switch to different therapies or combine fulvestrant with neratinib to get a longer disease-free status. The theme is using NGS and combining it with an increasing number of targeted therapeutics.

Health disparities – closing the gap

Terry Davis, PhD, a professor of medicine and pediatrics from Louisiana State University Health Sciences Center, reported on efforts to improve minority participation in clinical trials and biobanking. She noted that <1% of minority cancer patients are enrolling in clinical trials, and Dr. Barrett added that the death rate from all cancers is 25% higher for African Americans/blacks than for whites.

Dr. Davis' study of minorities found that there is a lack of awareness, understanding, trust, and acceptance of clinical trials. Dr. Barrett said that one thing AACR is doing to address this disparity is the "2020 by 2020" initiative – a commitment to sequence 2,020 genomics from African Americans/blacks by year 2020, and then to share the database around the country. And AACR is working with a historically black medical school, Morehouse School of Medicine, on outreach to the minority community.

Prevention – the link between chlamydia and ovarian cancer

A National Cancer Institute study found an association between prior infection with chlamydia trachomatis, and subsequent development of pelvic inflammatory disease (PID), and development of ovarian cancer. Using data from a Polish population-based case-control study and data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Britton Trabert, PhD, and colleagues found a ≥2.0 fold increase in ovarian cancer in women with prior chlamydia, "The kind of important message here is our data are lending support that there is a role for PID in ovarian cancer, and the primary cause of that, particularly in the U.S., is chlamydia infection.

Asked if there are any data showing that treating the chlamydia will prevent ovarian cancer, Dr. Trabert said, "We did not do that study." But she thought future studies should evaluate that.