Predicting Response to Endocrine Therapy in ER-Positive Breast Cancer

BY DIBASH KUMAR DAS, PHD

According to the American Cancer Society, nearly 70 percent of patients with breast cancer have hormone receptor-positive (HR+) disease—estrogen receptor-positive (ER+), progesterone receptor-positive (PR+), or both. Hormone therapy is designed to stop the effects of estrogen on the tumor and can be very effective for ER+ breast cancer. An assortment of drugs can be prescribed as hormone therapy, and clinicians choose a treatment regimen depending on the patient and the specifics of that person’s disease.

Aromatase inhibitors prevent the body from producing estrogen and are typically the first treatment of choice for hormone therapy, whereas other anti-estrogen drugs, such as fulvestrant, block the ER on cancer cells. However, there has historically been no reliable way to predict which patients will benefit, especially as the cancer advances or recurs.

Furthermore, in previous research, up to 50 percent of patients with HR+ breast cancer have not responded to first-line hormone therapy, and the occurrence of non-responsiveness increased during subsequent lines of hormone therapy (Lancet 2011; doi: 10.1016/S0140-6736(11)60993-8).

New research from the Washington University School of Medicine in St. Louis has found that an imaging test measuring the function of ERs in breast cancer cells can be used to distinguish between breast cancer patients who are likely, and those who are unlikely, to benefit from hormone therapy. The findings were published in Nature Communications (2021; https://doi.org/10.1038/s41467-020-20814-9).

In the small 5-year Phase II clinical trial (NCT02455453), Dehdashti and colleagues utilized an imaging agent that attaches to PRs on cancer cells. The compound, 21-[18F]fluorofuranylnorprogesterone (FFNP), attaches to PRs and can be detected with a positron emission tomography (PET) scan. When ERs are stimulated, the cells respond by increasing the number of PR molecules on their surfaces; however, there is no change in PRs if the ERs are inactive. The researchers observed the change in tumor uptake of the progestin analog 21-[18F] FFNP before and after a 1-day estradiol challenge. The team hypothesized that this short-term estradiol challenge would elevate tumor PR levels only among responders to FFNP, followed by three doses of estrogen over a 24-hour period and a second PET scan a day after the estrogen treatment. The researchers then followed the participants for 6 months or greater as they underwent hormone therapy as recommended by their physicians.

An increase in tumor FFNP uptake was observed in 28 patients with clinical benefit from hormone therapy, defined as no disease progression within 6 months. These patients were classified as responders, indicating that their ERs were working and had responded to the hormone by triggering an increase in PR numbers. Of the women whose tumors had responded, 13 remained stable and 15 improved.

Fifteen women showed little to no change in PR numbers after estrogen treatment; these women were classified as nonresponders. Each of the women were found to experience disease progression within 6 months of initiating endocrine therapy.

The median percentage change in tumor FFNP uptake among responders was 25.4 percent; in nonresponders, it was –0.7 percent. These findings demonstrate a 100 percent agreement between the response to estrogen challenge and the response to hormone therapy, even though the participants were on a variety of treatment regimens. No adverse or clinically detectable pharmacological effects were associated with FFNP administration. Additionally, there were no considerable changes in vital signs.

A larger Phase II clinical trial with collaborators at other institutions to verify the results is currently being set up, according to the researchers.

To gain additional insights into the study, Oncology Times spoke with lead author Farrokh Dehdashti, MD, Professor of Radiology in the Division of Nuclear Medicine of the Mallinckrodt Institute of Radiology at Washington University School of Medicine.

**Oncology Times:** What was the rationale for designing the imaging agent, [18F] FFNP, for ER-positive breast cancer patients? What were some of the factors which posed challenges in the development of the imaging method?

**Dehdashti:** “PR+ transcription is directly regulated by estrogen action through the ER, and the measurement of PR levels was originally proposed as a way to identify ER+ tumors with functional ER capable of mediating hormone therapy response. However, baseline tumor PR levels do not accurately predict response to hormone therapy. Accordingly, we hypothesized that the effect of a brief estradiol challenge on PR levels (measured noninvasively by PET with FFNP) would be a better biomarker of ER function and the likelihood of response to IT.

“Additionally, we recognized that PET with FFNP would provide an ability to address changing ER status in previously treated patients, obviating the need for biopsy to obtain tumor tissue for in vitro analysis of ER (an invasive procedure with associated risks and morbidity). Another likely advantage would be the ability to assess the ER status of all patient lesions by an imaging test, as multiple biopsies are rarely feasible.

“Because several previous attempts to develop PET imaging agents for PR had failed, several factors went into the specific design of FFNP. It was designed to have high affinity for PR and low non-specific binding to be resistant to metabolic inactivation by reduction of the C-20 ketone in prostogens, and to be rapidly and efficiently labeled with the short-lived PET radionuclide fluoride-18.”

Continued on page 25
in telehealth visits. Ravenell has successfully partnered with barbers to increase colorectal cancer screening among black men. “The barber shop is a place that we trust,” he said.

“Modern cancer treatment is precision medicine,” said Beverly Moyer, MD, MPH, Clinical Director of the Gillette Center for Women’s Cancers – Center for Breast Cancer at Massachusetts General Hospital. She noted that in many cases the best care option for a cancer patient is a clinical trial. She noted the reality is that U.S. health insurance plans vary widely in coverage, and some are quite limited, thus contributing to inequities in care. She also said biomarker tests often are not covered or it is unclear whether they are covered, adding that germline genetic testing should be done on family members who may be at higher risk, as well as the affected cancer patient. Agreeing was Jerrell Martin, RN, BSN, Clinical Specialist for Clinical Research and development at Bristol Myers Squibb. “An ideal health care system needs to recognize the value of personalized medicine,” said Martin.

Also agreeing was John Park, PharmD, Director of U.S. Oncology Marketing at Amgen, who decreed the fact that biomarker tests for targetable driver mutations are not being provided to all Americans. He said that fewer than one in four Americans is receiving biomarker testing for actionable and emerging mutations, and this gap is most pronounced in underserved populations. Park praised the cancer advocacy community, which he said “has done a lot to empower patients to seek biomarker testing.”

**Important Initiatives Needed**

Speakers at the ACS CAN Forum also discussed the following issues:

- Reimbursement for patient navigators in cancer care. “When you put trusted people in trusted places,” the health care system works better, said Ravenell.

- The need for cancer care providers to take the initiative in recommending a clinical trial to patients. People in underserved populations are not unwilling to participate in a clinical trial, but the system is stacked against their enrollment, said Mark Fleury, PhD, Principal for Policy Development & Emerging Science at ACS CAN. He said 80 percent or more of cancer patients will never be offered an invitation to enroll in a clinical trial. The FDA is actively working to bring more patients from underrepresented populations into clinical trials, and issued a guidance document on this topic in November 2020, said Rear Admiral Richardae Araojo, PharmD, Associate Commissioner for Minority Health and Director of the Office of Minority Health and Health Equity at the FDA.

- The need to take cancer clinical trials into the community. Now there is more of an emphasis on taking trials to the people by including them in non-academic centers, said Gregory J. Dennis, MD, Global Head of Therapeutic Science and Strategy Research and Development Solutions at IQVIA. An immunologist who helped start a community clinic while working at the National Institutes of Health, Dennis advocated for the use of resources for localized clinical trial sites far from the main research site. COVID-19 has taught cancer researchers about flexibilities in doing clinical trials at the local level, such as obtaining virtual remote consent, said Christopher S. Lathan, MD, MS, MPH, Director for Cancer Care Equity and Medical Director of the Dana-Farber Cancer Institute, Brighton.

- The need for continued reimbursement for telehealth treatment pathways. Many patients did not understand telehealth when the pandemic began, and now that it has become more routine, reimbursement for different telehealth applications (including audio-only consultations), should be continued when appropriate, said Mei Wa Kwong, JD, Executive Director of the nonprofit, nonpartisan Center for Connected Health Policy. She also said patients need a strong educational outreach effort in using telehealth, noting that her own father did not have a comfort level with it until she helped him.

Peggy Eastman is a contributing writer.

---

**ENDOCRINE THERAPY IN BREAST CANCER**

continued from page 23

**Oncology Times:** What are the clinical impacts of the findings of this study?

**Dehdashti:** “FFNP-PET before and after estradiol challenge can be accomplished in as little as 2 days prior to initiation of therapy and discriminates likely responders from nonresponders with high accuracy, thus allowing for risk stratification equivalent to that obtained by much longer clinical observations alone.”

**Oncology Times:** What additional factors need to be addressed before implementing this novel methodology into the clinic?

**Dehdashti:** “Our very encouraging single-institution results need to be confirmed by one or more larger multicenter trials, one of which has recently been funded. Ultimately, translation into the clinic will require interest by a radiopharmaceutical manufacturer, who will conduct the registration studies needed for FDA approval, and establish a production and distribution network for FFNP.”

**Oncology Times:** Is there a potential of transferability of this methodology for any other types of treatments?

**Dehdashti:** “It is possible that a similar strategy with PET imaging of an androgen receptor-regulated target protein before and after a hormone challenge with testosterone could be used to evaluate the function of androgen receptors in breast cancer and prostate cancer.”

Dibash Kumar Das is a contributing writer.