Pills Show Promise as an Alternative to Chemotherapy in CU Cancer Center Member's Breast Cancer Study

The trial of a three-drug cocktail is the first for a new research consortium of which the CU Cancer Center is a partner.

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The focus of a University of Colorado Cancer Center member's research career has been a quest for new, better therapies for patients with breast cancer. That quest by Elena Shagisultanova, MD, PhD, has resulted in a clinical trial pointing the way to an oral treatment that's more tolerable than intensive chemotherapy for patients with a type of metastatic breast cancer that accounts for about 20% of cases among women under age 45.

"Especially when women are young, usually they also work and have kids and they want to be active. They don't want to experience chemo side effects, hair loss, other physical changes, and severe fatigue associated with chemotherapy. We wanted a pure targeted therapy which is much milder compared to chemo," says Shagisultanova, associate professor in the Division of Medical Oncology at the University of Colorado School of Medicine.

Her study published Dec. 15 in Clinical Cancer Research – was the first to be completed as part of the Academic Breast Cancer Consortium (ABRCC). It's a new collaboration of the CU Cancer Center and several other leading research institutions, which states its goal as "expediting the process of identifying and efficiently testing active new compounds for the treatment of breast cancer."

The CU Cancer Center is Colorado's only ABRCC member. Peter Kabos, MD, another Cancer Center member and a professor of medical oncology at the CU School of Medicine, is its director.

The trial investigated combining a three-drug cocktail of oral treatments – tucatinib, letrozole, and palbociclib, and – to target HR+/HER2+ metastatic breast cancer, a form that disproportionately impacts younger women. Shagisultanova and co-investigators called this combination "TLP" for the first letters of each drug.

The result: TLP "showed excellent efficacy for an all-oral, chemotherapy-free regimen warranting further testing," the study says.

Countering crosstalk

Shagisultanova says her CU Cancer Center mentor, Virginia Borges, MD, steered her years ago toward specializing in young women with breast cancer. In her practice, she has encountered many breast cancer patients with the HR+/HER2+ subtype. HR+ cancer cells have receptors for the hormones estrogen or progesterone, which can spur growth of the tumor. HER2+ is a protein that also helps cancer cells grow quickly.

According to the National Cancer Institute, about 10% of new breast cancer cases between 2016 and 2020 were of the HR+/HER+ subtype. The five-year survival rate for the subtype ranges from 99.1% to 45.6% depending on the stage at diagnosis. NCI says. In young patients, this HR+/HER2+ breast cancer is more common (up to 20% of breast cancer cases in patients 45 years or younger), as Shagisultanova showed in her recent paper in Clinical Cancer Research.

Traditionally, treatment for such cancers has often involved intensive intravenous chemotherapy over an extended period. Shagisultanova has been seeking an effective oral alternative.

“When you have so many receptors essentially commanding the tumor cells to grow, it’s tempting to try to block them,” Shagisultanova says. But using two oral treatments targeting HR+ and HER+ specifically has been only “variably successful,” she says, because of complex molecular signaling “crosstalk” between the receptors that can thwart each drug’s effectiveness.

A 3-drug approach

The new study was aimed at showing that adding a third drug to the cocktail could improve effectiveness and provide a suitable all-oral alternative to chemotherapy. Lab work by Shagisultanova and Borges led them to think that tucatinib in combination with letrozole and palbociclib -- the TLP cocktail -- could produce even better results, as they reported in a 2022 paper.

Tucatinib is a targeted HER2 inhibitor, palbociclib is what’s known as a CDK4/6 inhibitor that stops cancer cells from rushing through the cell cycle required for fast growth, and letrozole is an anti-hormonal drug that restricts the ability of cancers to drive growth using estrogen. All are prescribed in tablet form.

In the TLP trial, 42 women ages 22 to 81 years were enrolled between 2017 and 2020, including some “pretty sick” patients and about 15 whose cancer had spread to the brain, Shagisultanova says. The trial was conducted at six ABRCC-member sites: the CU Cancer Center, University of Arizona, Northwestern University, University of New Mexico, Stony Brook University in New York, and University of Texas Health Sciences Center in San Antonio.

The study cites a clinical benefit rate for the three-drug treatment of 70.4%.

“Very, very early, it became apparent that the drug combination was working,” Shagisultanova

says. “We had several very long-term survivors who stayed on this combination for more than three years. I still have a patient who continues to be on this combination outside of the trial, after about five years, which we are very happy about.”

More agile and dynamic

Shagisultanova credits her CU Cancer Center colleague Kabos with being “very helpful and instrumental” with her research. And thanks to ABRCC’s involvement, “we recruited at all sites from the start and completed the study very quickly,” she says.

“Behind this consortium is that we really have to become much more agile and dynamic in the way we do clinical trials and accelerate getting drugs approved and getting them to patients,” she says.

Also providing key support for the study were the CU Cancer Center’s Developmental Therapeutics Program, Tumor Host Interactions Program, and Biostatistics and Bioinformatics Shared Resource.

Looking ahead, Shagisultanova hopes to extend study of the triple-combination treatment to patients in earlier stages of breast cancer “to see if we can shrink their tumors sufficiently to prepare them for surgery.”

Her research work is personal to her, she says.

“I went to a conference in San Antonio, and I saw cancer patient advocates standing with signs saying, ‘We are dying when you are discussing,’ and it’s very sad. We should really accelerate trials that bring novel therapies to patients.”

Shagisultanova says she is “very happy that I was able to help quite a few patients in the trial. Even if you make a difference in the life of one patient, it makes you happy.”

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