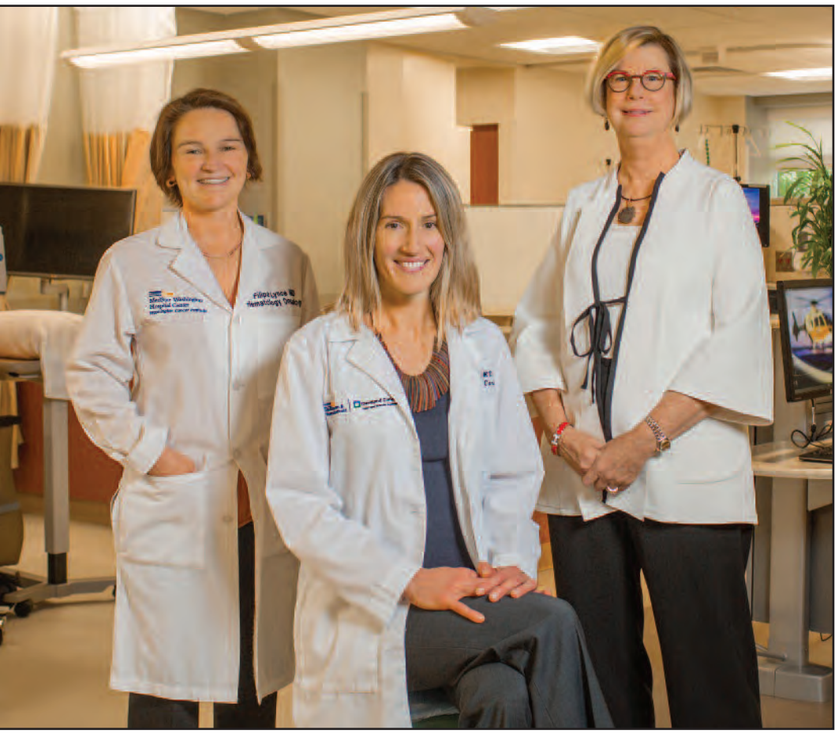
Cancer Therapy Benefits vs. Cardiovascular Risks

Pilot Study Seeks Right Balance Between Survival and Safety



Filipa Lynce, MD; Ana Barac, MD, PhD and Sandra Swain, MD, are leading the pilot study.

In a clinical trial spanning two hospitals and two specialties, MedStar Health physicians are studying how to maximize the use of highly successful targeted therapies for HER2-positive breast cancer, while minimizing adverse affects on the heart. If successful, the investigator-initiated study could open the door to the life-prolonging cancer regimen for a subset of patients who are currently denied access to its benefits.

The powerful class of cancer deterrents has an unintended, and unfortunate, consequence: 10 to 20 percent of those treated with the monoclonal antibody trastuzumab (Herceptin®) develop cardiovascular dysfunction. However, specialists have no way of knowing who might be affected.

As a result, trastuzumab, pertuzumab (Perjeta®) and other newer, related therapies are contraindicated for patients presenting with even mildly decreased left ventricular ejection fraction (LVEF). If the LVEF of a patient on the therapy dips by 10 percent from his or her baseline, or drops at any time below 50 percent, treatment must be stopped.

The dilemma lies in the lack of effective alternatives.

"Until the late 1990s, patients with HER2-positive breast cancer, who comprise up to 20 percent of all cases, faced an aggressive form of disease and a poor outcome," says Sandra M. Swain, MD, FACS, medical director of Washington Cancer Institute at MedStar Washington Hospital Center and principal investigator for study. "In trastuzumab, for the first time, we had a targeted treatment that worked wonders against most advanced and local disease. Yet its use was restricted because of its potential to harm the heart."

However, retrospective data and one small prospective study in patients with trastuzumab-induced cardiotoxicity have recently revealed that the damage is mostly short-lived and reversible. Those findings led Dr. Swain and her co-principal investigator Ana Barac, MD, PhD— a cardiologist at both the Hospital Center and MedStar Georgetown University Hospital, and director of the MedStar Heart & Vascular Institute's Cardio-Oncology program—to wonder if intensive monitoring and care could maintain heart function well enough for patients with borderline cardiovascular disease to complete a full course of HER2-targeted therapy.

In 2013, Drs. Swain, Barac and oncologist Filipa Lynce, MD, who wrote the protocol and received a grant from the American Society of Clinical Oncology for its implementation, launched SAFE-HEaRt to find out.

In this investigator-initiated study, the team recruits breast cancer patients with HER2-positive disease and mildly decreased heart function as determined by an LVEF between 40 and 49 percent, a cohort normally contraindicated for HER2-targeted therapy. Patients who are already receiving HER2 therapy when their ejection fraction drops below the 50 percent threshold are also eligible. All candidates are further evaluated through a stress test, echocardiogram and other diagnostics to rule out those with ischemia, valve problems, active heart failure and other cardiovascular conditions.

Trial participants follow a regimen of trastuzumab, pertuzumab and/or ado-trastuzumab emtansine (Kadcyla®)—alone or in combination, as dictated by stage of disease, along with standard cardiovascular monitoring and therapies, based upon extrapolation from heart failure trials. Approximately six weeks after starting cancer therapy, patients undergo another echocardiogram to check for changes in heart function, and are re-tested every three months thereafter. A final echocardiogram is administered six months after cancer therapy is completed. Throughout the study, all echocardiographic images are reviewed by MedStar Health Research Institute's Cardiovascular Core Lab.

"What sets SAFE-HEaRt apart is the involvement of cardiology from the very beginning," says Dr. Barac, who notes the trial is the only one of its kind in the nation. "Patients are followed throughout the study by both cardiologists and oncologists. As a result, the study coordination requires a huge amount of effort from multiple, extremely dedicated individuals."

SAFE-HEaRt's primary goal is to maintain or even improve each participant's LVEF concurrent with HER2 therapy to assure the safest and most optimal outcomes from both standpoints. In the process, however, the research team will also describe correlations between specific imaging and biomarkers and cardiac events, which may help identify patients at higher risk for HER2 therapy-induced damage in the future.

"Other studies continue to show that the monoclonal antibodies trastuzumab and pertuzumab produce a huge survival benefit for breast cancer patients with HER2-positive disease in either the advanced or adjuvant setting," says Dr. Swain. Indeed, the latest report, appearing in the February 19 issue of *The New England Journal of Medicine* and authored by Dr. Swain, found a median survival increase of 16 months for advanced disease.

"We hypothesize that these therapies are safe for patients with borderline or slightly diminished heart function when under a cardiologist's care," she concludes. "If we're right, we can rewrite the treatment guidelines for HER-2 positive breast cancer, and prolong even more lives." ■

—Leslie Whitlinger

Clinical Trial Needs Candidates

The SAFE-HEaRt team is seeking patients >18 years old, male or female, with HER2-positive breast cancer and mildly reduced LVEF. All patients will undergo additional cardiac testing before final selection. Those meeting requirements will be eligible to receive their planned HER2-targeted treatment, along with cardiac monitoring to safeguard their current and future health.

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