EDITORIAL

Adjuvant Capecitabine in Triple-Negative Breast Cancer
New Strategies for Tailoring Treatment Recommendations

Heather A. Parsons, MD, MPH; Harold J. Burstein, MD, PhD

Chemotherapy is an essential component of multidisciplinary treatment for estrogen receptor–, progesterone receptor–, and *ERBB2*-negative (ie, triple-negative) breast cancer and is critical for preventing tumor recurrence and improving long-term survival in this subset of tumors that accounts for 15% of breast cancers. Regimens that include 3 classes of chemotherapy drugs—anthracyclines, alkylators, and taxanes—represent the global standard of care for patients with triple-negative tumors, offering optimal cancer treatment. Traditionally, chemotherapy was given in the adjuvant setting after breast surgery. However, for women with stage II or III triple-negative breast cancer, preoperative or neoadjuvant chemotherapy is now preferred because it delivers systemic drug therapy and facilitates surgical downstaging, that is, reducing the tumor in the breast and axilla so that less extensive operations become options. Moreover, the extent of response to induction therapy can serve as an individualized, prognostic marker to guide subsequent treatment.[1]

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Capecitabine is an orally available, antimetabolite chemotherapy, a prodrug converted to fluorouracil. Multiple trials have explored adding capecitabine to standard chemotherapy regimens with the goal of improving existing options. One approach has been to "piggyback" capecitabine on top of standard anthracycline-, alkylator-, and taxane-based chemotherapy regimens. In triple-negative breast cancers, adding capecitabine concurrently with standard chemotherapy has been shown to reduce the risk of recurrence but substantially increase treatment toxicity without consistent improvements in overall survival.[2-4] Another strategy has been to add capecitabine sequentially after standard chemotherapy regimens. In the GEICAM 2003-11/CIBOMA 2004-01 study, which included 876 women, sequential therapy with 8 3-week cycles of capecitabine after standard adjuvant chemotherapy did not prevent recurrence of triple-negative breast cancer.[5]

Given these mixed outcomes, the data from the SYSUCC-001 study, reported by Wang et al[6] in this issue of *JAMA*, have been eagerly anticipated as a decisive trial for clarifying the role of capecitabine in triple-negative breast cancer. The trial included 434 women with triple-negative breast cancer, all of whom had received standard chemotherapy regimens. As is typical for triple-negative cancers, these tumors were high grade and had high rates of proliferation. Patients were randomized to no additional therapy (n = 221) or to treatment with 1 year of "metronomic" capecitabine (n = 222). The metronomic dose schedule refers to an uninterrupted administration of lower-dose chemotherapy. In this case, patients received about one-half of the usual daily dose of capecitabine (about 1000 mg twice a day), every day for a year, whereas other trials delivered more familiar schedules of capecitabine, comprised of cycles of a higher drug dose for 14 consecutive days, followed by a 7-day hiatus, for 6 or more cycles.

Women in the SYSUCC-001 trial had a better-than-anticipated outcome, a consistent finding in many contemporary adjuvant studies. The metronomic regimen significantly reduced the 5-year recurrence risk, an appropriate end point as most triple-negative cancers that are destined to recur do so within 5 years, with estimated disease-free survival rates of 82.8% in the capecetibine group and 73.0% in the group that received no additional therapy (hazard ratio, 0.64 [95% CI, 0.42-0.95]). Capecitabine treatment also resulted in a numerical (but statistically nonsignificant) advantage in overall survival: estimated 5-year survival, 85.5% in the capecetibine group and 81.3% in the no additional therapy group (hazard ratio, 0.75 [95% CI, 0.47-1.19]). These important clinical benefits extended to patients with node-negative disease (n = 268), who are considered to have a lower baseline risk than women with nodal involvement. The metronomic regimen also caused less fatigue, low blood counts, mucositis, diarrhea, and hand-foot syndrome than traditional capecitabine dosing, making the regimen well-tolerated by the standards of cancer drug therapy.

The findings from the SYSUCC-001 trial and other trials suggest that inclusion of capecitabine in addition to standard chemotherapy regimens can help women with triple-negative breast cancer achieve better outcomes in the long run. However, these results also invite important questions, such as how can patients who most warrant treatment be identified and how should capecitabine be administered?

Fundamentally, neoadjuvant systemic therapy aims to eliminate microscopic deposits of metastatic cancer that have disseminated from the primary tumor, and thus persist despite surgery and local radiation. Such foci of microscopic cancer—often called minimal residual disease (MRD)—are too small to detect on radiology scans or routine laboratory tests. Yet it is the eventual growth of such minute foci that ultimately accounts for tumor recurrence. The chance of MRD, and hence the need for systemic therapy in triple-negative breast cancer, is traditionally based on a probabilistic model (ie, the likelihood of MRD is proportional to anatomic stage) rather than determined by a patient-specific, direct test. But an individual patient either does, or does not, experience recurrence. With increasing efficacy of systemic treatments and related improvements in overall patient

outcomes, it becomes more important to identify individual patients who remain at risk. Conversely, treating a large population to benefit the relatively few patients at risk becomes less acceptable with longer duration of therapy, more toxicity, and greater cost.

Two developments may help identify patients at greatest risk for recurrence and thus most in need of extra chemotherapy. One approach for defining at-risk patients has been through the use of neoadjuvant therapy in triple-negative breast cancer. The amount of residual cancer after preoperative treatment, scored as a dichotomous yes/no or on a spectrum of response, is a powerful predictor of residual risk. Measurement of residual cancer burden quantifies residual disease after systemic neoadjuvant therapy and provides a prospectively validated, practical, continuous variable to estimate a patient's risk of recurrence.[7] When preoperative chemotherapy achieves total eradication of the tumor in the breast and lymph nodes (ie, a pathological complete response, or residual cancer burden score of zero), the prognosis is very favorable.[7,8] With increased burden of residual cancer, there is a progressively greater likelihood of recurrence.

Leveraging this individualized approach to risk stratification, and seeking to identify a cohort of higher-risk patients, the CREATE-X trial included 910 women who had received standard chemotherapy regimens in the preoperative setting and had residual invasive cancer despite the neoadjuvant treatments.[9] This degree of chemotherapy resistance left patients at greater risk for subsequent recurrence. In the CREATE-X trial, eligible patients were randomized to no further therapy or to 6 or 8 cycles of sequential capecitabine. Capecitabine therapy, compared with no further therapy, improved 5-year disease-free survival (70% vs 56%) and improved survival (78.8% vs 70.3%, respectively) in the cohort of 286 women with triple-negative tumors.

A strategy that is more speculative, although perhaps more promising, involves highly sensitive diagnostic tests that detect and measure minimal, persistent cancer burden as circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) through blood-based "liquid biopsy" assays. These assays have the power to measure the presence or absence of MRD in real time, potentially guiding therapeutic decision-making for an individual patient based on actual, rather than probabilistic, evidence of persistent cancer.

The presence of CTCs has previously been associated with less favorable prognosis in both early- and advanced-stage breast cancer. One CTC assay has been approved by the US Food and Drug Administration as a prognostic test in metastatic disease, even though the assay has more limited sensitivity for CTC detection in earlier stages of breast cancer, perhaps owing to a lower overall burden of tumor.[10] In a recent study, Radovich and colleagues[11] showed that among 123 patients with triple-negative breast cancer and residual cancer after preoperative systemic therapy and surgery, those with CTCs tended to have worse outcomes.

MRD measurement through ctDNA detection has shown even more encouraging results with respect to assay sensitivity, although this approach remains very early in clinical development. An early study by Garcia-Murillas and colleagues[12] showed a remarkably high likelihood of recurrence (100% at 3 years) among 13 patients with detectable ctDNA following curative neoadjuvant treatment and surgery. An analysis from the I-SPY2 neoadjuvant study platform involving 84 patients reported that persistence of ctDNA during neoadjuvant treatment was a marker for high (86%) risk of recurrence at 5 years, whereas clearance of ctDNA was associated with a much better prognosis, with only a 14% chance of recurrence, similar to outcomes following pathological complete response.[13] Lead times, the time from a positive test to clinical recurrence, have also increased,[14] with recent studies showing lead time of up to 39 months.[15] Given these findings, ctDNA technology is now being used in large, prospective studies to identify individual patients for additional, hopefully curative, cancer therapy in early-stage triple-negative breast cancer (NCT04434040 and NCT02101385).

As novel assays for MRD are being developed to identify particular patients with triple-negative breast cancer who warrant treatment beyond standard neo-/adjuvant chemotherapy, clinicians and patients must decide how best to utilize capecitabine. The data from the well-conducted SYSUCC-001 trial reported in this issue of *JAMA* bolster the growing literature that adding capecitabine after standard chemotherapy regimens offers meaningful benefit and an acceptable adverse effect profile for women with stage II or III triple-negative breast cancer. The preferred approach for women with stage II or III triple-negative tumors is neoadjuvant chemotherapy. The extent of tumor response can be used to guide recommendations for capecitabine, offering treatment to women with residual cancer and sparing those with complete pathological response from additional therapy. This strategy—informed by the collective experience in trials adding capecitabine, such as SYSUCC-001, and by the risk stratification and survival benefit in the CREATE-X study—seems to strike the right balance of offering more therapy to those most likely to benefit. Results from ongoing studies that are using molecular diagnostics to detect markers of residual risk are eagerly awaited, with the hope that they will allow more personalized treatment decisions informed by test results on every patient.

ARTICLE INFORMATION

Author Affiliations: Dana-Farber Cancer Institute, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Harold J. Burstein, MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215 (hburstein@partners.org).

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