Role of Capecitabine in Early Breast Cancer

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Systemic adjuvant or neoadjuvant chemotherapy, biologic, and hormone therapies have improved outcomes of patients with early-stage breast cancer. However, a substantial number of patients with early-stage breast cancer still develop recurrent disease, and there is need of additional improvement of systemic therapies. Triple-negative breast cancer (TNBC) comprises approximately 15% to 20% of all breast cancers and usually presents with a more aggressive clinical course and poorer outcomes compared with hormone receptor–positive and human epidermal growth factor receptor 2 (HER2) –positive breast cancer, leaving an unmet need for this patient population.¹ To date, no targeted therapies have been approved for the treatment of early-stage TNBC.

Capecitabine is an oral prodrug of fluorouracil, which is approved for the treatment of metastatic breast cancer and is effective after progression on anthracycline- or taxane-based regimens, suggesting that resistance mechanisms of those drugs are not overlapping.^{2,3} This provided the rationale for moving this agent to the adjuvant or neoadjuvant setting and combining it with standard anthracycline- and taxane-based regimens, which is the subject of the study by Lluch et al, which accompanies this editorial.⁴

Trials exploring the role of capecitabine monotherapy in the adjuvant setting demonstrated a lack of efficacy or inferiority to standard combination chemotherapy.^{5,6} In the ICE trial, patients older than age 65 years with early-stage breast cancer were randomly assigned to capecitabine or placebo in addition to a bisphosphonate for adjuvant therapy. There was no difference in 3- and 5-year disease-free survival (DFS) with the addition of capecitabine. Of note, three treatment-related deaths—of 668 patients—were reported in the capecitabine arm.⁵ In the CALGB 49907 trial, patients older than age 65 years with high-risk early-stage breast cancer were randomly assigned to receive adjuvant chemotherapy with capecitabine or standard combination chemotherapy (adriamycin/cyclophosphamide [AC] or cyclophosphamide/methotrexate/5-FU [CMF]). The study showed superior relapse-free survival (RFS) in the standard combination chemotherapy arm. Although patients receiving capecitabine had overall less toxicity, similar to the ICE trial, two treatment-related deaths were reported in the capecitabine arm.⁶

Several randomized controlled trials (RCTs) investigated the addition of capecitabine to standard adjuvant or neoadjuvant therapies.⁷⁻¹⁴ Limitations of some of these trials were a low-risk patient population¹⁰ or substituting a standard chemotherapy drug for capecitabine instead of adding capecitabine.^{7,11} Overall, most of these trials demonstrated no clinical benefit using capecitabine in the adjuvant or neoadjuvant settings. The FinXX trial⁹ was a well-designed phase III RCT in which patients were randomly assigned to receive docetaxel followed by epirubicin/cytosine, with or without the addition of capecitabine to docetaxel. RFS and overall survival (OS) did not differ significantly between the groups at the time of initial analysis at 4.9 years of follow up or after 10.3 years. However, in the preplanned exploratory subgroup analysis, significant improvement in RFS and OS was observed in the subgroup of patients with TNBC. Hazard ratio (HR) for death was 0.55 (95% CI, 0.31 to 0.96; $P = .03$) in the TNBC population.

The CREATE-X trial⁸ evaluated the addition of adjuvant capecitabine in a population of patients with HER2-negative breast cancer who had received standard neoadjuvant chemotherapy containing anthracycline, taxane, or both, and did not achieve pathologic complete response (pCR). The rationale for selecting this patient population was that pCR had been shown to be associated with increased DFS in most pathologic subtypes of HER2-negative breast cancer¹⁵ and may be considered a surrogate marker for survival. Therefore, the population of the CREATE-X trial was preselected to have an intrinsically worse prognosis. Patients were randomly assigned to standard post-surgical therapy with or without capecitabine. At 5 years, both DFS and OS were significantly longer in the adjuvant capecitabine group (DFS: 74.1% v 67.6%; HR, 0.7; 95% CI, 0.53 to 0.92; $P = .01$; and OS: 89.2% v 83.6%; HR, 0.59; 95% CI, 0.39 to 0.9; $P = .01$). In the prespecified subgroup analysis, the effect of capecitabine on survival was more prominent in the subgroup of patients with TNBC, which comprised 30% in both treatment and control groups (DFS: 69.8% v 56.1%; HR, 0.58; 95% CI, 0.39 to 0.87; and OS: 78.8% v 73%; HR, 0.52; 95% CI, 0.3 to 0.9). Capecitabine was well tolerated, with the most common expected adverse effect being hand foot syndrome. On the basis of the results of the CREATE-X trial, capecitabine is now included in the National Comprehensive Cancer Network breast cancer

ASSOCIATED CONTENT

See accompanying article on page 203

Author affiliations and support information (if applicable) appear at the end of this article.

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guidelines as adjuvant therapy for patients with TNBC with residual disease after neoadjuvant taxane, anthracycline, and alkylator chemotherapy. Building upon CREATE-X, the ongoing Eastern Cooperative Oncology Group–American College of Radiology Imaging Network study EA1131 (ClinicalTrials.gov identifier: [NCT02445391](https://clinicaltrials.gov/ct2/show/study/NCT02445391)) is evaluating the potential incremental benefit from adjuvant single-agent cisplatin or carboplatin over standard single-agent capecitabine in patients with TNBC who have not achieved pCR after neoadjuvant chemotherapy, particularly among those with a basal intrinsic subtype.

Two recent meta-analyses of major RCTs incorporating capecitabine in adjuvant or neoadjuvant therapy demonstrated a trend toward improved outcomes with the addition of capecitabine to the TNBC subgroups.^{16,17} The meta-analysis by Xu et al¹⁷ focused on 10 trials that added capecitabine to standard chemotherapy. Their study ($N = 12,872$) showed a numerically small, but statistically significant, benefit in DFS (HR, 0.84; 95% CI, 0.76 to 0.93; $P = .000$) and OS (HR, 0.84; 95% CI, 0.74 to 0.94; $P = .001$) with the addition of capecitabine in the overall population. In a subgroup analysis, the benefit was more prominent in patients with TNBC (DFS: HR, 0.77; 95% CI, 0.65 to 0.92; $P = .004$; and OS: HR, 0.65; 95% CI, 0.51 to 0.81; $P = .000$). The meta-analysis by Natori et al¹⁶ included 6 trials that investigated the addition of capecitabine and 2 trials that substituted standard treatments with capecitabine. In this meta-analysis of 9,302 patients, there was no improvement in DFS and OS in the overall population; however, there was an expectedly better effect on DFS and OS when capecitabine was added to standard chemotherapy rather than being used as monotherapy. Consistent with the results of the study by Xu et al,¹⁷ a subgroup analysis of four combination trials in the study by Natori et al¹⁶ showed that patients with TNBC derived significantly greater benefit from the addition of capecitabine compared with patients with non-TNBC (DFS: HR, 0.72 for TNBC v 1.01 for non-TNBC; interaction $P = .02$). Of interest, the two meta-analyses demonstrated discordant results regarding the effect of capecitabine in the general population, even though many of the trials in both studies were overlapping. This difference is perhaps because of the inclusion of the two capecitabine monotherapy studies in the meta-analysis by Natori et al,¹⁶ in particular the CALGB 49907 study, which showed inferiority of capecitabine compared with AC or CMF in patients with triple-negative disease. Conversely, the evidence of benefit with the addition of capecitabine in the meta-analysis by Xu et al¹⁷ was driven in part by the results of the CREATE-X trial and the study by von Minckwitz et al,¹⁴ which selected the population of poor responders to standard neoadjuvant chemotherapy.

The overall toxicity profile was tolerable across the trials¹⁶; however, when capecitabine was administered in combination with standard chemotherapy, rather than sequentially,

the combination arm required more frequent discontinuation of the standard chemotherapy, which could compromise treatment efficacy.¹² In addition, some trials were designed to include decreased doses of standard chemotherapy in the combination arms compared with control arms, which may confound the results of these studies.^{9,13}

Although the results of CREATE-X were practice changing, data are limited in that they are only applicable to patients who received neoadjuvant chemotherapy, which allows for selection and prognostication of patients by pathologic responses. However, not all patients are routinely treated with neoadjuvant therapy. Meta-analyses indicated that there is a signal toward an increased benefit of capecitabine combinations in patients with TNBC, although a relatively small proportion of patients with TNBC were included in the individual trials, and most trials were not powered to evaluate differences in this population. Therefore, the question remains as how to select patients who will benefit from the upfront addition of capecitabine, and prospective RCT data are needed to answer that question.

Lluch et al⁴ report a phase III RCT GEICAM/2003-11_CIBOMA/2004-01 investigating extended adjuvant treatment with capecitabine in patients with early-stage TNBC. Eligible patients received standard anthracycline- and/or taxane-based therapy and completed radiation therapy, if indicated, before enrollment. Patients were randomly assigned to receive capecitabine or observation. Capecitabine was administered in sequential fashion after completing standard chemotherapy, and not in combination. Patients were stratified on the basis of basal versus nonbasal molecular subtype (defined as a lack of staining for epidermal growth factor receptor and cytokeratins 5/6), with most patients (73%) having basal subtype, as expected in the TNBC population. With a median follow up of more than 7 years, both 5-year DFS (79.6% v 76.8%) and OS (86.2% v 85.9%) were not different between the capecitabine and placebo arms, respectively.

The results of the study by Lluch et al⁴ are somewhat discordant with the pooled evidence from prior trials, which showed a trend toward benefit by incorporating capecitabine with standard adjuvant or neoadjuvant chemotherapy in subgroups of patients with TNBC. Lluch et al⁴ focused on patients with TNBC and, to our knowledge, is the first phase III RCT specifically addressing the question of adding capecitabine in TNBC. Of interest, DFS and OS in the control group were higher than expected in the TNBC population based on historical data. This may be explained by a more favorable patient population compared with most other trials, including 55.9% of patients with node-negative disease. Excellent survival and a lower-than-expected recurrence rate in the control group make it difficult to demonstrate a difference between the control and experimental arms. In contrast, the CREATE-X trial preselected

patients with inherently high recurrence risk, predicted by relative resistance to the standard chemotherapy. In addition, the population of CREATE-X had more advanced disease, with only 39% of patients having pathologically node-negative disease after neoadjuvant chemotherapy.⁸ Thus, these two important trials cannot be directly compared, as they investigated different patient populations.

The finding of increased activity of capecitabine in the subgroup of patients with nonbasal TNBC in the study by Lluch et al⁴ is interesting and deserves additional investigation. Previous trials of adjuvant capecitabine did not address molecular phenotype; therefore, retrospective data for this question are not readily available.

Approximately 75% of TNBC tumors have basal-like molecular subtype, and 25% are nonbasal.¹⁸ TNBC can be further subclassified into Lehman's molecular subtypes.^{18,19} It has been shown that basal-like tumors have higher rates of pCR to anthracycline and taxane chemotherapy. Given the projected differences in pCR rates, it is possible that the population of the CREATE-X trial, selected by not having achieved pCR to the neoadjuvant therapy, was enriched with nonbasal subtype tumors. If the correlation between

nonbasal molecular subtype and increased response to capecitabine is validated, it could serve as a clinically useful molecular marker with which to identify patients who could benefit from upfront capecitabine. This, however, would require investigation in a prospective study or an analysis of the CREATE-X samples.

In conclusion, currently the only indication for the use of capecitabine in early-stage breast cancer is as post-neoadjuvant therapy in patients with TNBC who have not achieved pCR after standard neoadjuvant chemotherapy based on the CREATE-X trial. Current data do not support combining capecitabine with standard chemotherapy or its use as monotherapy for patients with early-stage breast cancer in the neoadjuvant or adjuvant setting. Going forward, it will be important to elucidate biomarkers with which to prospectively identify those patients for specific treatment strategies.

Lastly, novel approaches to TNBC are currently under investigation.¹ Immunotherapy was recently approved in metastatic TNBC,²⁰ and trials of immunotherapy in the neoadjuvant and adjuvant settings for early-stage TNBC are ongoing (ClinicalTrials.gov identifiers: [NCT02954874](https://clinicaltrials.gov/ct2/show/study?term=NCT02954874) and [NCT03036488](https://clinicaltrials.gov/ct2/show/study?term=NCT03036488)).

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