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ASO PERSPECTIVES

Assessment of Novel Therapeutics for Individualized Breast Cancer Care in the Modern Era: The Role of Metformin in Breast Cancer Therapy

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We live in an age of scientific discovery, where the landscape for optimal breast cancer care evolves continually. As breast cancer remains the most common cancer in women, breakthroughs in treatment can have an extensive global impact on women's health. While breast cancer remains the second leading cause of cancer-related mortality in this population, survival outcomes continue to improve with these ongoing therapeutic advances.[1] When practice-changing trial data are presented and published, the treatment algorithm from yesterday might now be outdated.

Yet, not all trials yield results that revolutionize breast cancer care. Despite promise in observational and laboratory studies, some potential therapeutics do not stand up when faced with a randomized controlled trial. In the era of evidence-based medicine, these treatments do not become standard practice. However, in considering study design and interpretation of results, one must also consider the spectrum of breast cancer itself. No breast cancer is created equal. These differences are clear in the expression of tumor markers, tumor genomics, staging, tumor pathology, patient genetics and demographics, and the tumor microenvironment and immune environment.[2] As such, we practice individualized breast cancer care, taking these factors into account in developing treatment pathways for each patient in the clinical setting. Accordingly, this diversity should also be considered in study design to optimize trial results and potential applicability, especially given all of the resources that must go into such a trial.

Considering this context, Goodwin et al. recently published the results from the MA.32 randomized clinical trial evaluating the effect of metformin given for 5 years in the adjuvant setting on invasive disease-free survival in non-diabetic patients with high-risk non-metastatic breast cancer undergoing curative-intent treatment.[3] Metformin is a medication commonly used in the treatment of type 2 diabetes. Preceding this trial's results, some observational studies suggested that metformin might improve breast cancer outcomes.[4–7] Additionally, preclinical laboratory studies further supported metformin's role in affecting oncologic signaling pathways.[8] While this precedence was promising, it is notable that there were some observational studies that did not support metformin's therapeutic potential.[9] Furthermore, in the metastatic breast cancer setting, randomized trials showed no oncologic survival benefit with the addition of metformin to standard regimens.[10,11]

The MA.32 randomized clinical trial, an international study of Goodwin et al., recruited non-diabetic patients diagnosed with high-risk breast cancer between 2010 and 2013. Patients were randomized to receive metformin or placebo for a total of 5 years after breast cancer surgery, and were then followed clinically through 2020. The primary outcome was invasive disease-free survival, and secondary oncologic outcomes included overall survival, distant relapse-free survival, and breast cancer-free interval. Notably, at the secondary interim analysis in 2016, metformin use in hormone receptor (estrogen and/or progesterone receptor) negative breast cancer patients was determined futile, and thus metformin use was stopped in this group. As such, final analysis only included hormone

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receptor positive patients (n = 2533). At the completion of the study, with a total of 465 primary events in this cohort, invasive disease-free survival was the same between the metformin group and the placebo group (2.78 vs. 2.74 per 100 patient-years, p = 0.93). There was no difference in secondary oncologic outcomes between the study arms, suggesting that metformin does not improve breast cancer outcomes in this patient population.[3]

Yet, while this study was ongoing, another phase II trial—the METTEN study—was pursued, investigating metformin's effect on pathologic complete response (pCR) rates for patients with HER-2 positive breast cancer receiving neoadjuvant therapy with metformin or placebo. Unfortunately, this trial's fate was in part driven by its inability to accrue. The results, albeit under-powered, showed no statistical difference in pCR rates related to neoadjuvant metformin use.[12] The authors did not stop there, however. Data out of Scotland have suggested that diabetic patients who have a particular single-nucleotide polymorphism (SNP) in their genetic code near the ataxia-telangiectasia mutated (ATM) gene, specifically the C allele of rs11212617, have enhanced glycemic control with metformin use compared with patients who do not have the C allele.[13] The relationship between genetic variation and drug efficacy has been described previously in relation to drug selection and dosing of both oncologic and non-oncologic medications.[14–16] Accordingly, genetic analysis was performed for patients included in the METTEN study to determine whether the C allele was associated with response to metformin. The authors found that presence of the C allele was in fact related to increased pCR rates in patients receiving metformin, but was not associated with response in those receiving placebo. These results, published in 2019, suggest that, in HER-2 positive breast cancer, neoadjuvant metformin use was related to improved treatment response in patients with the C allele.[17]

With these data in mind, Goodwin et al. conducted a post hoc analysis of the study population of MA.32, stratifying by HER-2 positivity and presence of the aforementioned C allele. They found that, in the HER-2 positive population, metformin use was associated with improved invasive disease-free survival compared with placebo (1.93 vs. 3.05 events per 100 patient years; HR, 0.64; 95% CI 0.43–0.95; p = 0.03) and improved overall survival. In a subset analysis of the HER-2 positive population based on presence of C-allele, metformin use was only associated with these improved oncologic outcomes in patients with the C allele. HER-2 negative patients did not benefit from metformin use based on the study's primary and secondary outcomes.[3]

At first glance in reading the conclusions of the MA.32 study's abstract, it may appear to some that there is no role for metformin in breast cancer treatment for non-diabetic patients. However, thoughtful post hoc analysis could suggest otherwise in certain populations, though additional study is needed. A call for pursuit of more data is a common and appropriate, yet somewhat unsatisfying, way to conclude an analysis of a therapeutic clinical trial that has required extensive resources and has been years coming to fruition. In this modern era of science and medicine, could there be another way to potentially optimize phase III clinical trial design to allow for more fruitful results?

The I-SPY 2 study has introduced a novel phase II trial design into the breast cancer arena, with a goal of rapidly identifying promising therapies and launching them into phase III studies with increased confidence in their ultimate therapeutic potential. This study is for patients with high-risk non-metastatic breast cancer with a primary outcome of pCR. Adaptive randomization is applied to place patients in the most appropriate neoadjuvant treatment arm based on patient- and tumor-specific variables, as well as ongoing study results. This design allows for simultaneous assessment of multiple potential breast cancer therapies with maximal treatment effect.[18] Cortazar et al. previously suggested that there is a relationship between pCR and long-term oncologic outcomes.[19] Tumor response to neoadjuvant therapy essentially provides a prognostic window to look forward toward the patient's survival outcomes. Thus, rather than wait years to measure these long-term survival outcomes for every potential therapeutic agent that comes down the line, instead, at the time of surgery, pCR could be used as an immediate surrogate for oncologic drug utility and candidacy for further study. The I-SPY 2 trial beautifully integrates this concept, along with adaptive randomization of patients into study groups based on breast cancer subtype to optimize and individualize study results.[18] This in a way represents the future of the breast cancer field: continued rapid therapeutic evolution based on advanced scientific pursuit for personalized breast cancer care. As a clinician, when I help guide each patient's journey through breast cancer treatment, I continue to be hopeful and inspired as I see more and more paths toward cure. In the end, regarding the outcomes of the MA.32 trial, metformin could be one of the tools down that path for certain patients, but additional study is needed.

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