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CORRESPONDENCE

Beyond *HER2* and Trastuzumab: Heterogeneity, Systems Biology, and Cancer Origin Research May Guide the Future for Personalized Treatment of Very Early but Aggressive Breast Cancer

TO THE EDITOR: In the December 1, 2009, issue of *Journal of Clinical Oncology,* Gonzalez-Angulo et al,[1] assessing high risk of recurrence among some women with T1a,bN0M0 breast cancer, conclude that for these women with *HER2*-positive disease, an adjuvant systemic trastuzumab-based therapy should be considered. Current recommendations do not consider such a treatment in these patients.[2,3] Given that in contrast to trastuzumab efficacy in more advanced stages,[4] no direct evidence for such a therapeutic effect exists for *HER2*-positive pT1a,bN0M0 tumors, could this report from M.D. Anderson Cancer Center[1] be considered a changing-practice study?

The vast majority of patients with breast tumors ≤ 1 cm (pT1a,b) and negative lymph nodes (pN0) have an excellent prognosis. As a result, generally no adjuvant systemic treatment is recommended at this early stage (pT1a,bN0M0).[2,3] But some patients recur and die from the disease. The biologic and genetic basis of this metastatic recurrence capacity has been poorly understood. Therefore, currently no robust markers to predict high-risk patients have been discovered and no effective therapeutics have been developed to prevent treatment failure.[5]

In an effort to identify and effectively treat patients at high risk of recurrence among those with very small breast tumors, Gonzalez-Angulo et al[1] performed a retrospective analysis of clinicopathologic treatment and follow-up data of 965 patients with pT1a,bN0M0 breast cancer. Ten percent (n = 98) had a *HER2*-positive disease and the remaining 867 patients had a *HER2*-negative tumor. No patient received adjuvant systemic chemotherapy and trastuzumab after local treatment. At a median follow-up of 74 months, there were 51 recurrences in *HER2*-negative and 21 recurrences in *HER2*-positive groups. The absolute 5-year recurrence rates were 23% and 6.3% in patients with *HER2*-positive and *HER2*-negative tumors, respectively ($P < .001$). In multivariate analysis, the relative risk of recurrence was significantly higher among *HER2*-positive patients (HR, 2.68; 95% CI, 1.44 to 5.0; $P = .002$).

Why are there some concerns regarding the authors' conclusion that current guidelines should change? First, the absence of randomization and the retrospective nature of this study. Second, the rarity of events (recurrence, death) at this early pT1a,bN0 stage requires a much larger number of patients than the 98 *HER2*-positive patients for appropriate Kaplan-Meier survival curves comparison between the *HER2*-positive and *HER2*-negative groups. Third, even smaller was the number of hormone receptor–positive patients (n = 60) within the *HER2*-positive group, and no data are provided whether tamoxifen treatment in these women could reduce recurrence risk. Fourth, a longer follow-up is needed. Fifth, no *HER2*-positive patient received trastuzumab in this study, and no conclusion can be made on its efficacy considering also lack of such data at this early stage in current medical literature. Sixth, the data of this study are inconsistent with that of another current report.[6] In the Istituto Europeo di Oncologia Milano (IEOM) study,[6] in contrast to the M.D. Anderson Cancer Center report, the overall 5-year recurrence risk for *HER2*-positive patients (n = 150) was low and ranged between 1% for hormone receptor–positive and 8% for hormone receptor–negative women. There was no significant difference between *HER2*–positive and *HER2*–negative groups (HR, 2.4; 95% CI, 0.9 to 6.5; $P = .09$).

These contrasting results and the scarce data explain the rarity of both *HER2*-positive disease (7% to 12%) in pT1a,bN0M0 disease and treatment failure events (recurrence, death).[1,6,7] This makes it difficult to perform future randomized controlled trials to assess the efficacy of chemotherapy—trastuzumab treatment for *HER2*-positive and endocrine therapy for hormone-responsive tumors at this very early stage. But even if such treatment will be proven effective, resistance to trastuzumab and tamoxifen[8] or aromatase inhibitors and lack of markers to predict high-risk women suggest a major challenge.

Personalized recurrence risk prediction and appropriate treatment prevention looks to be an excellent future perspective. The key in this approach may lie in understanding why only a few women among those with a pT1a,bN0M0 tumor experience recurrence. Cancer heterogeneity with the presence of resistant subclonal cell populations even within an individual tumor is widely accepted.[9] But what kind of cells are these with aggressive behavior and nonsensitivity to current therapies?

Among various theories, two concepts are now more often discussed and supported by preliminary experimental findings. The cancer stem cells theory is supported by preclinical studies,[10,11] but scientific evidence for cancer stem cells–based clinical implications is still scarce. Both the existence of tumor-initiating cells and the potential for future development of agents targeting Wnt, Notch, and other developmental signaling pathways for treating currently refractory breast, melanoma, and other solid cancers is currently controversial.[12,13]

Another, perhaps more hopeful approach, is the concept of mutated gene-gene interactions and signaling pathways networks.[14] Although at very early stage, such as pT1a,bN0M0, more than five to seven mutations are required, which are estimated to be needed for transformation of a normal cell to cancer cell; this number is significantly lower than the approximately 60 to 100 driver mutations involved in advanced breast, colorectal, and pancreatic cancer.[15] The hypothesis of a genetic network may explain recurrence and death at this very early stage. Despite a limited number of driver mutations at pT1a,bN0M0 stage, the inference of specific gene interactions may result in an aggressive genotype-phenotype relationship.[16] If it is true, what's next? In the era of next-generation DNA sequencing technology and cancer genomes,[17] we hope for the completion of a driver mutation cancer catalogue and the understanding of gene functions

and their interaction (causal network) prediction.[14-17] The development of novel network modeling provides promises for a genotype-phenotype–based personalized treatment of breast cancer and other solid tumors.[16,18]

But in the real world of a day-to-day clinical practice, how could we now approach possible appropriate decision making for women with pT1a, bN0M0 breast cancer? First, all useful information regarding current, standard prognostic factors including age, tumor size (T1a *v* T1b), grade (1, 2 *v* 3), *HER2*, and hormone-receptor status,[2,3] and the latest advances and controversies with micrometastases and/or isolated tumor cell sentinel and nonsentinel lymph nodes[19,20] and multigene assays (Oncotype DX, Genomic Health Inc, Redwood City, CA; MammaPrint, Agendia BV, Amsterdam, the Netherlands)[5,21] should be collected. Second, all of this information and current controversy regarding the efficacy of trastuzumab and tamoxifen or aromatase inhibitors at very early stages should be evaluated and interpreted carefully. Third, discussion with individual patients about the risk of recurrence and adverse effects of chemotherapy and targeted therapy is needed. Ultimately, balancing these estimated risks and benefits, a personalized approach can be achieved on the basis of an algorithmic approach.[5] Currently, treatment of women with pT1a,bN0M0 tumors is extremely complex and requires discussion between a multidisciplinary expert team and the individual patient.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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