correspondence

The 5-Year Paradigm in DCIS of the Breast: Unexpected Lessons From the NSABP B-43 Trial

TO THE EDITOR:

Cobleigh et al[1] have reported on the phase III NSABP B-43 trial. This unique randomized cohort provides the first data on the effectiveness of a dual dose of trastuzumab when added to adjuvant whole-breast irradiation after lumpectomy for human epidermal growth factor receptor 2–positive ductal carcinoma in situ (DCIS).[1] As the number of ipsilateral breast tumor recurrences (IBTRs) in this extensive cohort was lower than originally estimated, the initially proposed 36% reduction in the IBTR hazard ratio was not achieved.[1] Although not statistically significant, adjuvant trastuzumab was nevertheless associated with a 19% reduction in IBTRs. Subgroup analysis showed that this was because of a marked reduction in in situ IBTRs, without effect on invasive IBTRs.[1] Although the authors mentioned two explanations, we would like to highlight another interpretation of this observation.

The authors hypothesized that trastuzumab might somehow block the progression of DCIS to invasive breast cancer, as they observed more in situ than invasive IBTRs (66.7% *v* 33.3%, respectively). Although it is possible that invasive IBTRs in this cohort were too scarce to identify a potential benefit from trastuzumab on invasive recurrence risk, we believe that this observation is not because of chance or lack of power. Many randomized controlled clinical trials and retrospective studies showed higher numbers of in situ IBTRs than invasive IBTRs within the first 5 years of follow-up, such as the SweDCIS trial.[2,3] Long-term follow-up results in a 50/50 distribution of in situ and invasive recurrences.[3-5] Consequently, the median time to develop in situ IBTRs is generally shorter than the median time to invasive IBTRs.[6] We previously observed a tipping point at 5 years of follow-up in the curve of in situ recurrences in a recent report on the UK Sloane Project, whereas the slope of the invasive recurrences' curve remained unchanged.[6] Future studies should therefore explicitly differentiate between short-term (< 5 years) versus long-term (> 5 years) recurrence risk, as well as between in situ and invasive IBTR risk. Median follow-up in the B-43 trial was 79.2 months (ie, 6.6 years). It may be worthwhile to await long-term follow-up data, whereafter the cumulative incidence of in situ and invasive IBTRs should be plotted separately per treatment arm. These data were not provided in the present report,[1] but it might be too early to perform such an analysis. We expect a similar 5-year tilting angle in the in situ IBTR curve after 10 years of follow-up, whereas the invasive IBTR curve will probably show a stable slope. This difference could be explained by the origin of IBTRs.[7] We surmise that most in situ IBTRs represent outgrowths of residual DCIS after initial lumpectomy, despite the achievement of negative margins (defined as no ink on tumor). The in situ IBTR curve within the first 5 years of follow-up therefore probably reflects the completeness of the initial surgery. Additionally, some so-called invasive IBTRs arise de novo, and are clonally unrelated to the initial DCIS, whereas other invasive IBTRs arise from residual DCIS after incomplete initial lumpectomy.[7] It would be worthwhile to evaluate this 5-year paradigm in the well-balanced B-43 cohort since patients were stratified according to menopausal status, hormonal treatment, and nuclear grade, representing three potentially confounding factors. Remarkably, nuclear grade was not associated with IBTR risk in the B-43 trial.[1]

This unique human epidermal growth factor receptor 2–positive DCIS cohort provides excellent opportunities to investigate to what extent IBTRs are clonally related with initial DCIS. This could teach us lots about the risk of developing a true IBTR. It is assumed that many types of DCIS are in fact biologically indolent and unable to evolve to invasive carcinoma. The possibility exists that DCIS is a mere risk factor for developing invasive cancer, without being the obligatory noninvasive precursor. This divergent scenario could elucidate the past difficulties to identify robust prognostic markers for IBTR as we are yet unable to distinguish both types of recurrence risk from one another. To date, no large-scale data are available to clarify this enigma, although early attempts were made by morphologic, immunohistochemical, and copy number analyses.[8-10] Future research should combine clinical-radiologic, histopathologic, immunohistochemical, and molecular data to determine the precise relation between DCIS and subsequent IBTRs. Such a study will likely have a major influence on the present clinical management of patients with DCIS.[7]

In conclusion, a 6.6-year 19% reduction of in situ IBTR by trastuzumab is a clinically spectacular result, given that all B-43 patients were irradiated, which is known to halve the IBTR risk after lumpectomy. The lack of impact on invasive IBTRs could be because of the lack of a clonal relationship with the primary DCIS.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Cobleigh MA, Anderson SJ, Siziopikou KP, et al: Comparison of radiation with or without concurrent trastuzumab for HER2-positive ductal carcinoma in situ resected by lumpectomy: A phase III clinical trial. J Clin Oncol 39:2367-2374, 2021
2. Emdin SO, Granstrand B, Ringberg A, et al: SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol 45:536-543, 2006
3. Warnberg F, Garmo H, Emdin S, et al: Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 Years follow-up in the randomized SweDCIS trial. J Clin Oncol 32:3613-3618, 2014
4. Wapnir IL, Dignam JJ, Fisher B, et al: Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 103:478-488, 2011
5. Donker M, Litiere S, Werutsky G, et al: Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-Year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol 31:4054-4059, 2013
6. Van Bockstal MR, Libbrecht L, Galant C: Comment on: "Pathological features of 11,337 patients with primary ductal carcinoma in situ (DCIS) and subsequent events: Results from the UK Sloane Project." Br J Cancer 124:1461-1462, 2021
7. Van Bockstal MR, Agahozo MC, Koppert LB, et al: A retrospective alternative for active surveillance trials for ductal carcinoma in situ of the breast. Int J Cancer 146:1189-1197, 2020
8. Zhou W, Johansson C, Jirstrom K, et al: A comparison of tumor biology in primary ductal carcinoma in situ recurring as invasive carcinoma versus a new in situ. Int J Breast Cancer 2013:582134, 2013
9. Gorringe KL, Hunter SM, Pang JM, et al: Copy number analysis of ductal carcinoma in situ with and without recurrence. Mod Pathol 28:1174-1184, 2015
10. Visser LL, Elshof LE, Van de Vijver K, et al: Discordant marker expression between invasive breast carcinoma and corresponding synchronous and preceding DCIS. Am J Surg Pathol 43:1574-1582, 2019

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