San Antonio Breast Cancer Symposium 2022

Title: Characterization of recurrence risk after lumpectomy and radiotherapy in HER2-positive ductal carcinoma in situ of the breast, using 7-gene predictive biosignature: Implications for the NSABP-B43 trial results

Background: HER2-positive versus HER2-negative ductal carcinoma in situ (DCIS) of the breast has been associated with an increased risk of local recurrence after breast-conserving surgery (BCS) and radiotherapy (RT). In recognition of this, the NASBP-B43 trial was designed to determine if two doses of trastuzumab would improve local control with BCS plus RT in HER2-positive DCIS. The trial demonstrated a non-statistically significant advantage with the addition of trastuzumab in reducing ipsilateral breast recurrence (IBR). The predictive 7-gene DCIS biosignature, DCISionRT with Residual Risk Subtype (PreludeDx TM, Laguna Hills, CA)has been shown to classify DCIS patients into two distinct groups of patients with substantially different rates of IBR following BCS plus RT. Based upon these differences in outcome, we assessed the IBR rate in patients with HER2(+) DCIS treated with BCS and RT who were or were not in the Residual Risk Subtype group defined using DCISionRT, while accounting for the varying clinicopathologic profile of the patients.

Methods: DCISionRT was evaluated in a subset of 178 women with HER2(+) DCIS treated with BCS and RT as part of a multinational cohort of 926 patients from the United States, Sweden, and Australia, who were used in the validation studies for DCISionRT. Central pathology review and biosignature testing were performed at a CLIA-certified lab (Laguna Hills, CA). HER2(+) DCIS was defined as patients with a HER2(3+) immunohistochemistry >10% per ASCO/CAP guidelines. The IBR rate was calculated for the overall group of HER2(+) patients and those in the Residual Risk group. Individual patient outcome and biosignature results were analyzed using Kaplan Meier and Cox Proportional Hazard analyses.

Results: The biosignature classified 113 of the 178 (63%) HER2(+) women into the Residual Risk group (DS>2.8with RRt). Patients in the Residual Risk group had a significantly greater IBR (HR=8.3; 95%CI: 1.1,50, p=.012) over 10-years, with a corresponding 10-year total IBR rate of 16.2% (95%CI: 9.7%, 26.5%) versus 1.6% (95%CI:0.2%, 10.9%) for all other HER2(+) patients.

In univariate analysis, younger patients tended to have higher IBR rate after BCS plus RT, but only Residual Risk was significantly associated with IBR rate after BCS plus RT. Moreover, multivariable analysis demonstrated that the Residual Risk group was eight times more likely to recur after BCS and RT, while clinicopathologic factors (age, grade, tumor size) were not associated with higher IBR rates.

Conclusion: The DCISionRT Residual Risk group was predictive for 10-year IBR risk after BCS plus RT in women with HER2(+) DCIS. Approximately 40% of patients with HER2(+) DCIS would be expected to achieve low rates of recurrence with BCS and RT, while about 60% of these women (classified in the Residual Riskgroup) would have higher recurrence rates and may benefit from further therapy, such as HER2-directed therapies. These findings suggest that if the results of the B43 trial were re-analyzed using the predictive 7-gene biosignature (DCISionRT with Residual Risk Subtype), better clarity could be gained on the true impact of trastuzumab on IBR rates in patients with HER2(+) DCIS and the patients most likely to benefit from this additional therapy.

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Table 1. Univariate and Multivariable Cox Proportional Hazards Analyses

	Multivariable		Univariate	
Factors	**HR 95% CI**	**p value**	HR 95% CI	**p value**
Biosignature Residual Risk Group (vs Low and Elevated Risk groups)	7.9 (1.0, 63)	0.048	8.5 (1.1, 67)	0.038
Extent >10mm (vs ≤ 10 mm)	2.4 (0.8, 7.1)	0.17	2.8 (0.7, 5.8)	0.16
Grade 3 (vs Grade 1 and 2)	1.0 (0.2, 4.7)	0.98	1.8 (0.4, 8.1)	0.42
Age <50 (vs ≥ age 50)	2.6 (0.9, 7.5)	0.07	2.4 (0.9, 6.7)	0.09

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