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Brief Communication

Antimullerian Hormone as a Serum Biomarker for Risk of Chemotherapy-Induced Amenorrhea

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Abstract

Antimullerian hormone (AMH) is a promising biomarker for ovarian reserve. In this study, we assessed AMH before and 1 year after initiation of adjuvant chemotherapy on National Surgical Adjuvant Breast and Bowel Project (NSABP)/NRG Oncology B-47 in female participants aged 42 years and younger (median age = 39 years). At baseline, median AMH was 1.2 ng/mL; 13 (4.7%) values were less than 0.1 ng/mL (the threshold for detectable levels, in the perimenopause and menopause range), and 57 values (20.6%) were less than 0.5 ng/mL. At 1 year, 215 (77.6%) were less than 0.1 ng/mL, and 264 (95.3%) were less than 0.5 ng/mL. Postchemotherapy menses were reported by 46.2% of participants. Multivariable logistic regression found that the odds of having postchemotherapy menses increased with younger age, higher body mass index, and higher prechemotherapy AMH, but not by trastuzumab administration or by the choice of chemotherapy (doxorubicin-cyclophosphamide followed by paclitaxel vs docetaxel-cyclophosphamide). We conclude that higher prechemotherapy AMH predicts a lower risk of chemotherapy-induced amenorrhea and that AMH 1 year after chemotherapy initiation is not informative in this setting because it is likely to be very low.

The more than 50 000 premenopausal women diagnosed annually in the United States with breast cancer are vulnerable to long-term treatment toxicities including menopausal symptoms and infertility (1–3). Chemotherapy-induced amenorrhea (CIA) is associated with poorer ovarian function and reduced fertility, although many patients who experience short-term CIA do later menstruate (4). It is difficult to counsel young women about their risk of CIA, although older age and higher doses of gonadotoxic chemotherapy are known to increase risk (5–9), and some studies suggest that lower body mass index (BMI) does too (10). Small studies have suggested that a lower prechemotherapy level of serum antimullerian hormone (AMH), a glycoprotein produced by the ovarian granulosa cells, may predict a higher likelihood of CIA (4,10–16). Here, we assessed how prechemotherapy and postchemotherapy AMH are associated with CIA in NSABP/NRG Oncology B-47, a trial that rigorously collected patient-reported data on menses.

The B-47 trial randomly assigned patients with early-stage HER2-low breast cancer who provided informed consent to receive adjuvant trastuzumab or not, concurrent with either anthracycline-cyclophosphamide and taxane (AC-T) or docetaxel and cyclophosphamide (TC) (17). In an analysis that was planned while the trial was ongoing (and added to the internal review board-approved protocol), we measured pre- and post-chemotherapy AMH on all 282 B-47 participants who were diagnosed at age 42 years or younger and who had serum stored before chemotherapy and at 1-year follow-up after being randomly assigned. We did not include older patients because CIA

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Table 1. Patient characteristics with row percentiles shown[a]

Characteristic	Ever-reported menstruation after chemotherapy, No. (%)		Total No.
	No	Yes	
Total	149 (53.8)	128 (46.2)	277
Race			
White	121 (54.3)	102 (45.7)	223
Black	14 (58.3)	10 (41.7)	24
Asian	7 (38.9)	11 (61.1)	18
Other	7 (58.3)	5 (41.7)	12
Age at diagnosis, y			
24-35	21 (30.4)	48 (69.6)	69
>35-40	66 (52.4)	60 (47.6)	126
>40-42	62 (75.6)	20 (24.4)	82
BMI, kg/m^2			
16.5-20	9 (75.0)	3 (25.0)	12
>20-25	49 (54.4)	41 (45.6)	90
>25-30	54 (57.4)	40 (42.6)	94
>30-59.8	37 (45.7)	44 (54.3)	81
Nodal status			
pN0	22 (43.1)	29 (56.9)	51
pN1	83 (53.2)	73 (46.8)	156
pN2	34 (63.0)	20 (37.0)	54
pN3	10 (62.5)	6 (37.5)	16
Hormone receptors			
ER and PR negative	15 (34.9)	28 (65.1)	43
ER and/or PR positive	134 (57.3)	100 (42.7)	234
Chemotherapy			
AC-T	112 (52.1)	103 (47.9)	215
TC	37 (59.7)	25 (40.3)	62
Study arm			
No trastuzumab	65 (52.0)	60 (48)	125
Trastuzumab	84 (55.3)	68 (53.1)	152
Tamoxifen use (ever)			
Unknown	15 (34.9)	28 (65.1)	43
No	14 (73.7)	5 (26.3)	19
Yes	120 (55.8)	95 (44.2)	215

[a]AC-T = doxorubicin-cyclophosphamide followed by paclitaxel; BMI = body mass index; ER = estrogen receptor; PR = progesterone receptor; TC = docetaxel-cyclophosphamide.

prediction is most clinically relevant during child-bearing years. None of the 282 participants were missing menses data or had received gonadotropin-releasing hormone agonist (GNRHa) before 12 months follow-up. Serum AMH was evaluated by an Ansh Ultra-Sensitive AMH enzyme-linked immunoassay, a quantitative 3-step sandwich immunoassay (18).

The primary endpoint was postchemotherapy menstruation, defined as the report of at least 1 period between 6 and 12 months after random assignment and at repeated follow-up visits up to 3 years after random assignment (including surveys that were returned as late as 42 months). Because the 6-month assessment would have captured menses that occurred prior to receipt of chemotherapy (because chemotherapy duration was approximately 4–5 months), we excluded 6-month data from the analyses. Any data collected after recurrence, death, hysterectomy, or bilateral salpingo-oophorectomy were censored. GNRHa use within the first 12 months was an exclusion criterion, and data were censored for those using GNRHa after 12 months.

We evaluated if age, prechemotherapy AMH, chemotherapy regimen, BMI, receipt of trastuzumab, and receipt of tamoxifen were associated with occurrence of menses. To evaluate the association of these variables with menses at the repeated follow-up visits (considering presence or absence of 1 or more menstrual periods during each 6-month time frame as a binary variable), we used a logistic regression mixed model (R software glmer) with random intercepts for subjects to account for within-subject correlations of longitudinal follow-up indicators of menses. Two-sided P values of less than .05 based on Wald statistics were considered statistically significant. After removing errors and missing values, there were 277 patients with AMH at baseline and 12 months who had menses information available at 1 or more qualifying follow-up visits. AMH values below the lower limit of detection (<0.1 ng/mL) were set to 0.05 ng/mL. With 277 patients included, we had more than 80% power to detect a minimum odds ratio (OR) of 1.5, where the odds ratio represents the change in risk of CIA according to 1 standard deviation change in the prechemotherapy AMH.

Median age of the eligible participants was 39 years. Seventeen (6.1%) had data from time points after 12 months censored due to receipt of GNRHa. Other characteristics are presented in Table 1. Menses had occurred at least once over the prior 6 months in 31.4% of 277 eligible respondents at 12 months, 41.3% of 230 at 18 months, 40.8% of 218 at 30 months, and 52.2% of 207 at 36 months; 46.2% of the 277 women reported menses on at least 1 of their available assessments from months 12 to 42.

Table 2. Multivariable model for menses after chemotherapy

Covariate	Odds ratio (95% CI)	P[a]
Age, y		
<35	1.00 (Referent)	
>35-40	0.53 (0.30 to 0.94)	.03
>40-42	0.14 (0.07 to 0.29)	<.001
Tamoxifen		
No	1.00 (Referent)	
Yes	0.74 (0.42 to 1.29)	.29
BMI, kg/m^2		
>20-25	1.00 (Referent)	
<20	0.27 (0.08 to 0.96)	.04
>25-30	0.98 (0.56 to 1.72)	.95
>30	1.86 (1.04 to 3.32)	.04
Chemotherapy		
AC-T	1.00 (Referent)	
TC	1.20 (0.68 to 2.12)	.52
Trastuzumab		
No	1.00 (Referent)	
Yes	0.82 (0.52 to 1.30)	.41
AMH at baseline[b]	1.24 (1.12 to 1.37)	<.001

[a]Wald statistic 2-sided *P* value. AC-T = doxorubicin-cyclophosphamide followed by paclitaxel; AMH = antimullerian hormone; BMI = body mass index; CI = confidence interval; OR = odds ratio; TC = docetaxel-cyclophosphamide.
[b]As a continuous variable. *P* value was calculated using Wald statistic 2-sided *P* value.

At baseline, the median AMH was 1.2 ng/mL (range = 0.5-6 ng/mL; interquartile range = 0.6-2.6 ng/mL). Of the 277 AMH levels, 13 (4.7%) were less than 0.1 ng/mL, and 57 (20.6%) of the 277 AMH levels were less than 0.5 ng/mL. At 1 year, 215 (77.6%) levels were less than 0.1 ng/mL, and 264 (95.3%) were less than 0.5 ng/mL. We focused our modeling on the prechemotherapy AMH rather than on change in AMH because the magnitude of the change would be the same as the prechemotherapy level for most patients.

Our multivariable logistic regression (Table 2) showed that the odds of having postchemotherapy menses increased with younger age (OR = 0.14, 95% confidence interval [CI] = 0.07 to 0.29; $P < .001$ for age 35 years and younger vs 40-42 years), higher BMI (OR = 1.86, 95% CI = 1.04 to 3.32; $P = .04$ for BMI > 30 vs >20-25), and higher prechemotherapy AMH (OR = 1.24, 95% CI = 1.12 to 1.37; $P < .001$). In contrast, the specific chemotherapy regimen (TC vs AC-T), trastuzumab receipt, and tamoxifen use were not associated with postchemotherapy menstruation. There were too few patients with non-White race to evaluate race/ethnicity as an independent variable in the model. Among the 9 women aged older than 40 years with an undetectable AMH at baseline, 2 (22.2%) went on to report menstruation on at least 1 of the 12- to 36-month surveys.

We confirmed the findings of prior small studies that AMH, age, and BMI before chemotherapy could help predict a woman's risk of CIA. However, 1/5 of those with both undetectable AMH and aged older than 40 years before they started chemotherapy did go on to menstruate postchemotherapy, highlighting the limitations of this biomarker. More than 3/4 of 1-year AMH levels were undetectable, making change in AMH or postchemotherapy AMH not useful as independent predictors of amenorrhea (because the magnitude of the change is usually the same as the prechemotherapy level). Despite the low postchemotherapy AMH values, subsequent menstruation occurred in nearly half of patients. Therefore, AMH approximately 7-8 months after the completion of chemotherapy should not be used to predict likelihood of return of ovarian function later, at least for these young patients. Data on estradiol and follicle-stimulating hormone from the larger premenopausal cohort of B-47 will further inform our findings. Furthermore, our results demonstrate that although some anthracycline-sparing regimens may not be substantially gonadotoxic, TC is not one of them. Our long-term goal is to develop an actionable risk model for CIA that will incorporate genetic variation, serum biomarkers, and clinical variables; this will be facilitated by the inclusion of rigorous menstrual and hormonal assessments in other clinical trials.

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Data Availability

All de-identified data generated or analyzed during this study is available upon request.

References

1. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. The effects of paclitaxel, dose density, and trastuzumab on treatment-related amenorrhea in premenopausal women with breast cancer. *Cancer*. 2010;116(4):791–798.
2. Swain SM, Land SR, Ritter MW, et al. Amenorrhea in premenopausal women on the doxorubicin-and-cyclophosphamide-followed-by-docetaxel arm of NSABP B-30 trial. *Breast Cancer Res Treat*. 2009;113(2):315–320.

3. Ganz PA, Land SR, Geyer CE, Jr., et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. *J Clin Oncol*. 2011;29(9):1110–1116.
4. Passildas J, Collard O, Savoye AM, et al. Impact of chemotherapy-induced menopause in women of childbearing age with non-metastatic breast cancer - preliminary results from the MENOCOR study. *Clin Breast Cancer*. 2019;19(1):e74–e84.
5. Abusief ME, Missmer SA, Ginsburg ES, Weeks JC, Partridge AH. Relationship between reproductive history, anthropometrics, lifestyle factors, and the likelihood of persistent chemotherapy-related amenorrhea in women with premenopausal breast cancer. *Fertil Steril*. 2012;97(1):154–159.
6. Zhang B, Wu J, Zheng R, et al. Evaluation of menopausal status among breast cancer patients with chemotherapy-induced amenorrhea. *Chin J Cancer Res*. 2018;30(4):468–476.
7. Shin JJ, Choi YM, Jun JK, et al. Amenorrhea and menopause in patients with breast cancer after chemotherapy. *J Breast Cancer*. 2019;22(4):624–634.
8. Koga C, Akiyoshi S, Ishida M, Nakamura Y, Ohno S, Tokunaga E. Chemotherapy-induced amenorrhea and the resumption of menstruation in premenopausal women with hormone receptor-positive early breast cancer. *Breast Cancer*. 2017;24(5):714–719.
9. Zavos A, Valachis A. Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. *Acta Oncol*. 2016;55(6):664–670.
10. Su HC, Haunschild C, Chung K, et al. Prechemotherapy antimullerian hormone, age, and body size predict timing of return of ovarian function in young breast cancer patients. *Cancer*. 2014;120(23):3691–3698.
11. Anders C, Marcom PK, Peterson B, et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. *Cancer Invest*. 2008;26(3):286–295.
12. Anderson RA, Rosendahl M, Kelsey TW, Cameron DA. Pretreatment anti-mullerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer. *Eur J Cancer*. 2013;49(16):3404–3411.
13. Ruddy KJ, O'Neill A, Miller KD, et al. Biomarker prediction of chemotherapy-related amenorrhea in premenopausal women with breast cancer participating in E5103. *Breast Cancer Res Treat*. 2014;144(3):591–597.
14. Zec I, Tislaric-Medenjak D, Megla ZB, Kucak I. Anti-mullerian hormone: a unique biochemical marker of gonadal development and fertility in humans. *Biochem Med*. 2011;21(3):219–230.
15. Xue C, Wei W, Sun P, et al. Pretreatment anti-mullerian hormone-based nomogram predicts menstruation status after chemotherapy for premenopausal women with hormone receptor-positive early breast cancer. *Breast Cancer Res Treat*. 2019;173(3):619–628.
16. Palinska-Rudzka KE, Ghobara T, Parsons N, Milner J, Lockwood G, Hartshorne GM. Five-year study assessing the clinical utility of anti-mullerian hormone measurements in reproductive-age women with cancer. *Reprod Biomed Online*. 2019;39(4):712–720.
17. Fehrenbacher L, Cecchini RS, Geyer CE Jr, et al. NSABP B-47/NRG Oncology Phase III Randomized Trial Comparing Adjuvant Chemotherapy With or Without Trastuzumab in High-Risk Invasive Breast Cancer Negative for HER2 by FISH and With IHC 1+ or 2. *J Clin Oncol*. 2020;38(5):444–453.
18. Gruson D, Homsak E. Measurement of anti-mullerian hormone: performances of a new ultrasensitive immunoassay. *Clin Biochem*. 2015;48(6):453–455.