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Original article

Anti-Müllerian hormone (AMH) levels in premenopausal breast cancer patients treated with taxane-based adjuvant chemotherapy – A translational research project of the SUCCESS A study

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ABSTRACT

Background: Premenopausal women undergoing chemotherapy are at high risk for premature ovarian failure and its long-term consequences. Data on potential markers to evaluate ovarian reserve pre- and posttreatment are limited. Anti-Müllerian hormone (AMH) known for ovarian reserve in reproductive medicine could be a surrogate marker and was assessed in premenopausal breast cancer patients of the SUCCESS A study (EUDRA-CT no. 2005-000490-21).

Methods: We identified 170 premenopausal patients, age ≤ 40 years at trial entry, who received FEC-Doc as taxane-anthracylince based chemotherapy. Blood samples were taken at three time points: Before, four weeks after and two years after adjuvant chemotherapy. Serum AMH-levels were evaluated in a central laboratory by a quantitative immunoassay AMH Gen II ELISA (Beckman Coulter, Brea, USA).

Results: Median age was 36 years (21–40 years). Median serum AMH-level before chemotherapy was 1.37 ng/ml (range < 0.1–11.3 ng/ml). Four weeks after chemotherapy AMH-levels dropped in 98.6% of the patients to <0.1 ng/ml (range < 0.1–0.21 ng/ml).

After two years, 73.3% (n = 101) showed no evidence of ovarian function recovery (AMH <0.1 ng/ml, range < 0.1–3.9 ng/ml). Permanent chemotherapy induced amenorrhea occurred only in 50.6% of the patients.

Conclusions: In this analysis, premenopausal patients showed a high rate of ovarian impairment reflected by low AMH-levels after chemotherapy.

1. Background

Breast cancer is the most common malignancy in women worldwide and although it mostly occurs in postmenopausal women approximately 25% of breast cancer patients are affected in their reproductive age [1,2].

Adjuvant chemotherapy improves overall survival especially in breast cancer patients with an increased risk of recurrence [3] and is therefore frequently applied in patients aged <40 [4]. However, undergoing adjuvant chemotherapy is associated with ovarian suppression and persistent ovarian failure resulting in infertility

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and premature menopause.

Moreover, ovarian failure is causing osteoporosis, increased cardiovascular risks and loss of libido in a relevant number of patients. Especially fertility issues and unfulfilled desire for children concern patients [5].

Predictive factors for ovarian failure after chemotherapy are still lacking. Also, the exact mechanism, how chemotherapy affects ovarian reserve, is not well understood but seems to result in depletion of primordial follicle oocyte reserve [6–8]. Chemotherapy-induced amenorrhea was evaluated for alkylating agents, such as cyclophosphamide [9], but data are conflicting concerning the use of relevant chemotherapy regimens today. It remains unclear, whether additional taxanes cause a higher risk for gonadal impairment than the use of anthracyclines and alkylating agents alone [10–13].

From the point of reproductive medicine, the estimation of chemotherapy-induced amenorrhea rates is not sufficient to evaluate ovarian reserve. This is not only important for covering fertility issues but also to choose the right adjuvant endocrine treatment. Anti-Müllerian Hormone (AMH) provides a valid insight into ovarian reserve since it is a secretion product throughout the follicle development from the primordial to the early antral follicle. Comparing Inhibin B, estradiol, Follicle Stimulating Hormone (FSH), and AMH-levels, AMH offers the best correlation to the number of antral follicles [14]. Single parameter determination is in the clinical context more practicable to assess ovarian reserve. Therefore, AMH is regarded to surpass the above cited hormones [15,16].

Given the high clinical relevance of fertility issues in younger breast cancer patients and the lack of long term data of uniformly treated cohorts, we investigated the ovarian reserve in the SUCCESS A translational research project. Therefore, we evaluated AMH-levels in premenopausal patients with early breast cancer before and after adjuvant anthracycline and taxane-based chemotherapy, as well as during follow-up.

2. Methods

2.1. Study design

The German SUCCESS A trial is an open-label, multicenter, randomized controlled, Phase III study, evaluating the benefit of adding gemcitabine to an anthracycline and taxane-based adjuvant chemotherapy for primary breast cancer patients, as well as the disease-free survival after two vs. five years of Zoledronate [17]. Patients randomized required to present axillary lymph node metastases (pN1-3) **or** high-risk node negative disease, defined as pT $\geq$ 2 **or** histopathological grade 3, **or** age $\leq$ 35 **or** negative hormone receptor status, but were not allowed to have evidence of distant metastases. All patients had undergone surgical treatment (breast conserving or mastectomy) leading to R0 resection of the primary tumor. The study was approved by the ethics committees and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained of all patients before study inclusion.

2.2. Treatment

Between September 2005 and March 2007, 3754 newly diagnosed breast cancer patients were randomly assigned to the following: Either 3 cycles 5-Fluorouracil (5-FU) 500 mg/m^2, Epirubicin 100 mg/m^2, Cyclophosphamide 500 mg/m^2 (FEC) q3w followed by 3 cycles of Docetaxel (D) 100 mg/m^2 or 3 cycles FEC q3w followed by 3 cycles of Docetaxel 75 mg/m^2 q3w and Gemcitabine 1000 mg/m^2 day 1 and 8 q3w. In a second randomization, all patients had two vs- five years of Zoledronate (4 mg q3m for 24 months vs. 4 mg q3m for 24 months, followed by q6m for 36 months). Loco-regional radiotherapy was delivered in case of breast conserving surgery or criteria defining high-risk for loco-regional relapse. Patients with estrogen and/or progesterone positive tumors were assigned to a treatment of Tamoxifen 20 mg daily for 5 years. Hormone receptor positive patients additionally received gonadotropin-releasing hormone (GnRH) analogues (Goserelin®) 3.6 mg s.c. q4w, if they presented premenopausal hormone levels after chemotherapy, were under the age of 40 years or resumed regular menstrual cycles within 6 months after completion of chemotherapy. Administration for ovarian protection during chemotherapy was at the discretion of the physician.

2.3. Patients

For this analysis we only included premenopausal patients, who entered the SUCCESS A study aged 40 or younger and were randomized to FEC-Doc, regardless of bisphosphonate treatment duration. Patients receiving gemcitabine according to protocol were not considered for this analysis in order to prevent the bias of different cytotoxic regimens and due to the fact that gemcitabine has no role in current adjuvant treatment regimens. The kinetic of AMH values impacted by FEC Docetaxel based chemotherapy corrected for age by univariate and multivariate regression was assessed.

Women were stratified premenopausal at baseline if they reported regular menses during the 12 months prior to randomization. Assessment of ovarian function by LH, FSH and estradiol testing during study participation was not mandatory. Follow-up data concerning relapse, administration of concomitant therapy, i.e. endocrine treatment and the incidence of amenorrhea (yes/no) were obtained every 3 months for the first 3 years after chemotherapy, switching to 6 monthly in year 4 and 5.

A translational research project was carried out within the SUCCESS A study. Blood sampling was scheduled for every participating patient at predefined times during the study: Prior to, four weeks after and two years after chemotherapy, during follow-up respectively.

The peripheral blood samples were shipped to the Laboratory for Tumorimmunology at the Department of Gynecology and Obstetrics of the University Hospital Munich.

AMH analysis was performed by an external laboratory, using a commercial ELISA test (Beckman Coulter, Brea, USA). The lowest detection limit value was determined to be 0.08 ng/ml with a 95% probability.

2.4. Statistical analyses

Statistical analyses were performed with the programming language R version 2.11.1. Univariate linear regression models were used to estimate the impact of age on AMH-levels. Multivariate linear regression models were performed to evaluate the impact of tumor characteristics on AMH-levels. We did not include lifestyle factors like smoking or the prior use of contraceptives and treatment for infertility, as these information were not documented sufficiently in the clinical case report forms in this trial as in most other studies deigned at the time of study initiation. Wilcoxon signed-rank test was carried out to measure the relation of AMH-levels after chemotherapy to menstrual patterns.

3. Results

3.1. Patient characteristics

Documented serum AMH-levels as well as follow-up data were

available in 170 patients at both time points before, and immediately after chemotherapy. The number of available serum samples taken at follow-up two years after chemotherapy was 101. The median age at diagnosis was 36 years (range 21–40 years). Patient characteristics at study entry are listed in Table 1. 49% of the patients had a tumor stage pT1 and 55% were node positive. 69% were estrogen and/or progesterone receptor positive and 29% were HER2 positive.

3.2. Serum AMH-levels

Before chemotherapy, median serum AMH-level was 1.37 ng/ml (SD 2.12; range <0.1–11.3). After chemotherapy, we observed a rapid decrease of AMH below the threshold of detection (<0.1 ng/ml) in 98.6% (SD 0.01; range < 0.1–0.21 ng/ml). Two years after completion of adjuvant cytotoxic treatment the number of available serum samples were 101. Findings indicate a slight increase of AMH in a small proportion of patients, whereas serum levels remained low in 73.3% (mean < 0.1 ng/ml, SD 0.46; range < 0.1–3.9 ng/ml). 27 patients showed AMH-levels above the threshold of 0.1 ng/ml, whereas only 4 of them presented with "normal" serum levels ≥1 ng/ml by reproductive means (see Fig. 1).

Younger age was associated with higher pre-treatment AMH-levels. Median AMH in patients ≤35 years (n = 71) was 1.76 ng/ml (range < 0.1–8.28 ng/ml; SD 2.02) compared to a median serum AMH of 1.21 ng/ml (range < 0.1–11.32 ng/ml; SD 2.15) in the 99 women older than 35 years. At the end of cytotoxic treatment, serum levels were similar for both age subgroups with a mean AMH of 0.1 ng/ml. Two years after chemotherapy AMH was lower in patients >35 years, with a mean AMH of 0.17 ng/ml (range < 0.1–1.62 ng/ml; SD 0.27) compared to a mean AMH of 0.3 ng/ml in patients ≤ 35 years (range < 0.1–3.9 ng/ml; SD 0.65) (Fig. 2) However, this was not statistically significant.

Table 1
Patient characteristics.

Variables	n = 170	(%)
Age (years)	median: 36, mean: 35.8	
Tumor Size		
pT1	83	48.8%
pT2	81	47.7%
pT3	4	2.4%
Unknown	2	1.2%
Nodal Status		
pN0	77	45.3%
pN1	69	40.6%
pN2	17	10.0%
pN3	7	4.1%
Hormone Receptor Status		
Negative	52	30.6%
Positive	118	69.4%
HER2/neu Status		
Positive	49	28.8%
Negative	120	70.6%
Unknown	1	0.6%
Grading		
G1	5	2.9%
G2	79	46.5%
G3	85	50.0%
Unknown	1	0.6%
Adjuvant Endocrine Therapy		
Tamoxifen (TAM)	15	8.8%
TAM + Goserelin	90	52.9%
Goserelin	1	0.6%
None	64	37.7%
Ovarian Protection during Chemotherapy		
Yes	12	7.1%
No	185	92.9%

Age was the strongest predictor for AMH-levels prior to chemotherapy. In univariate analysis, higher age at study entry was significantly associated with lower AMH-levels with a decrease of 0.13 ng/ml per life year (p = 0.003). This finding was consistent in the multivariate analysis, showing only age as a variable influencing AMH-levels (p = 0.0078), whereas no association to classical prognostic markers, such as tumor stage, lymph node involvement, receptor status, etc. was observed.

In contrast, age did not directly correlate with serum AMH two years after chemotherapy. Only women with higher AMH-levels at baseline were likely to have elevated levels during follow-up (p < 0.001) (Table 2).

3.3. AMH-levels and amenorrhea

Permanent chemotherapy-induced amenorrhea occurred in 86 patients (50.6%). 49.4% (n = 84) resumed their menses with at least one documented menstrual bleeding during follow-up. There was no association between the patients' AMH-level and their menstrual pattern after chemotherapy. Higher AMH-levels before chemotherapy were not predictive for a shorter chemotherapy-induced amenorrhea period (p = 0.56) and women who remained amenorrheic were not likely to present with lower AMH-levels two years after chemotherapy (p = 0.42).

3.4. AMH-levels and adjuvant endocrine therapy

106 of the 118 hormone receptor positive patients received adjuvant endocrine treatment after chemotherapy. The combination of Tamoxifen and GnRH analogues was administered in 90 cases (52.9%), 15 patients (8.8%) received Tamoxifen alone. One patient (0.6%) was treated with GnRH analogues alone.

Patients on Tamoxifen had the same follow-up AMH-levels like patients without (p = 0.28).

In contrast, patients with combined endocrine treatment (Tamoxifen + ovarian suppression by GnRH analogues) during the follow-up period showed lower AMH-levels by a mean of 0.24 ng/ml when compared to women without endocrine treatment (p = 0.01) at all. These findings were independently confirmed in the multivariate analysis (Table 2).

4. Discussion

We evaluated serum samples in 170 premenopausal breast cancer patients aged 40 or younger at the time of primary diagnosis that underwent adjuvant chemotherapy. We observed a significant decrease in AMH-levels after cytotoxic treatment. The ovarian reserve in 101 patients remained impaired after a follow-up period of two years, with only four patients showing serum AMH-levels ≥ 1.0 ng/ml, which in general indicates a sufficient ovarian function by reproductive means.

These findings are in line with current data on serum hormone concentrations measured in premenopausal breast cancer patients [10,18–21]. Anderson et al. also found a decrease in AMH concentrations during chemotherapy examining 42 patients receiving different chemotherapy regimens. AMH-levels remained significantly low for a year after cytotoxic treatment. They found that pretreatment serum AMH, FSH, antral follicle count, and age predicted late ovarian activity by univariate analysis. However, only AMH was predictive in a multivariate analysis [21].

Although we found a very low number of patients with AMH recovery, resumption of menstrual bleeding occurred in 49.4% of the participants, demonstrating limited association between AMH-levels and menstrual pattern after chemotherapy. These findings are in line with other data and suggest that although menstruation

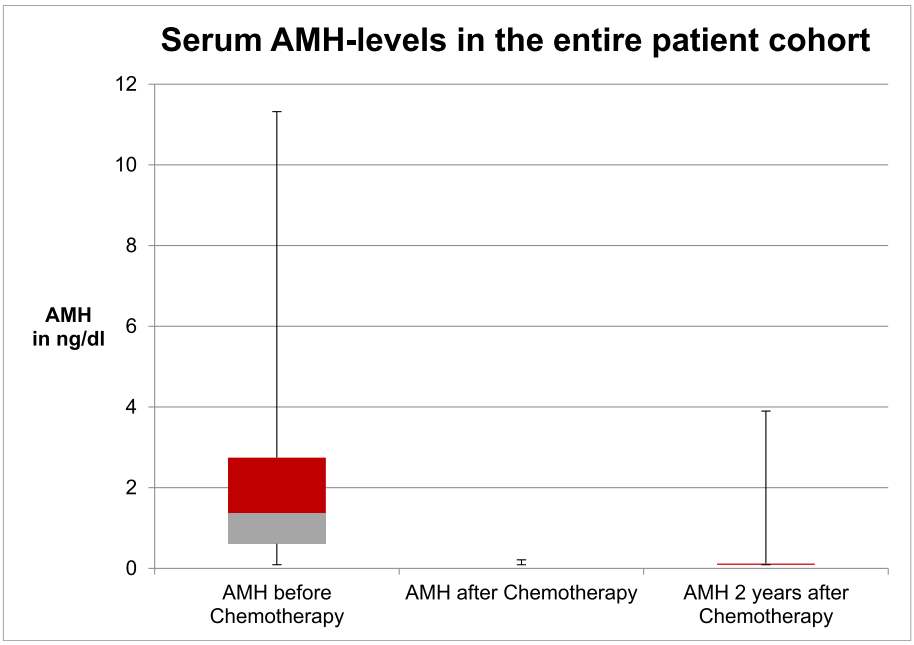

Fig. 1. Serum AMH-levels before chemotherapy and after two years in the entire patient cohort.

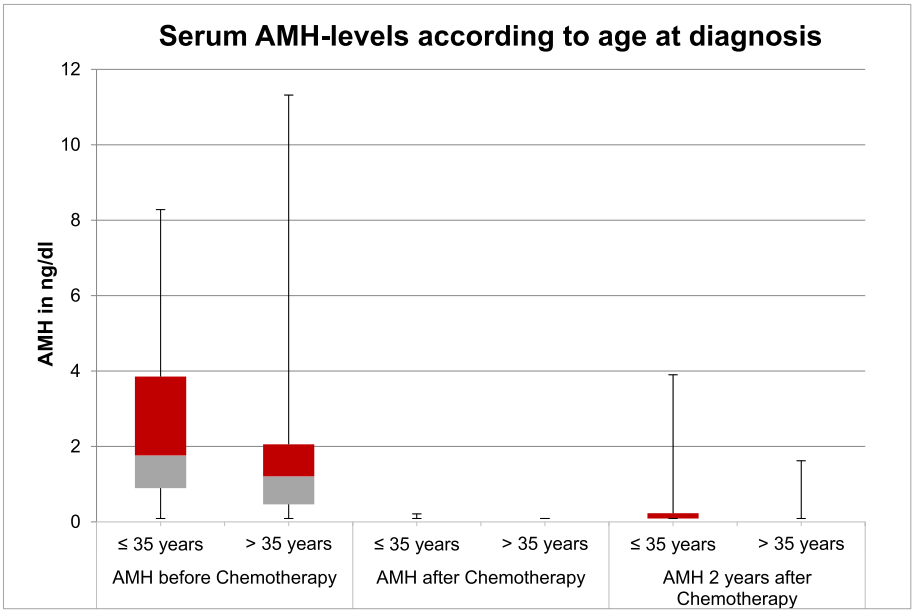

Fig. 2. Serum AMH-levels at three time points according to age at diagnosis.

Table 2
Multivariate linear regression analysis.

Variables	Serum AMH two years after Chemotherapy	
	Estimate	P-Value
Age per life year	−0.01	0.34
Serum AMH before Chemotherapy	0.09	<0.001[a]
Endocrine Therapy (TAM vs. none)	−0.19	0.28
Endocrine Therapy (TAM + Goserelin vs. none)	−0.24	0.01[a]

[a] Statistically significant.

takes place the ovarian reserve has been reduced [22,23]. It might be explained by the hypothesis that the absolute count of primordial oocytes is impaired in number and quality, although the ovaries seem to continue working still properly. In average pregnancy rates are 40% lower in cancer survivors compared to the general population, which clearly supports ovarian impairment [24]. Unfortunately, we lack data beyond breast cancer follow-up. It might be conceivable, that AMH deficient patients enter menopause distinctly earlier than their female relatives.

Furthermore, our results indicate that patients with higher baseline AMH concentrations tend to have higher AMH concentrations post chemotherapy as a predictor for higher ovarian reserve. This is consistent with findings from a study of Dezellus

et al., who investigated 250 young breast cancer patients at age 18–39 years receiving adjuvant/neoadjuvant chemotherapy. significant decline in AMH was seen from 4.19 ± 4.84 ng/ml prior to undetectable after the chemotherapy. Like in our data they observed that chemotherapy-induced amenorrhea was seen in patients with lower basal AMH-levels and older age [18]. Rosendahl et al. reported similar data with again initial AMH decline and undetectable AMH-levels during cytotoxic treatment. During follow-up, those patients with pretreatment serum levels above the median regained significant higher AMH-levels ($p = 0.001$) and antral follicle counts ($p = 0.05$) [25].

Like in prior research, AMH concentrations before chemotherapy did not predict the incidence of chemotherapy-induced amenorrhea, nor did the levels at follow-up correlate with the duration of chemotherapy-induced amenorrhea in our patient cohort [23]. Nevertheless, Anders and Rosendahl observed significant low baseline AMH-levels in premenopausal breast cancer patients who suffered from persistent chemotherapy-induced amenorrhea, while post chemotherapy AMH did not differ between amenorrheic and menstruating participants [25,26]. According to the meta-analysis of Frèour et al. women suffering from chemotherapy-induced amenorrhea also tend to be older besides presenting with lower baseline AMH-levels [10].

All patients were treated with taxane-based chemotherapy and chemotherapy-induced amenorrhea rate (50.6%) was similar to other studies, suggesting no pronounced harm of taxanes to the ovaries. This is in line with results of Reh et al. and Zavos et al. who investigated the use of taxanes in terms of ovarian impairment and found no significant effect on amenorrhea rates [12,13], while Frèour et al. and Zhao et al. clearly demonstrate a negative impact on the ovaries [10,11].

Tamoxifen did not seem to influence AMH-levels, supporting that AMH is not dependent on gonadotropin secretion. Dezellus et al. also found no association with tamoxifen use and Su et al. found similar post chemotherapy AMH-levels in patients who received adjuvant Tamoxifen and were matched to a cohort of hormone receptor negative breast cancer patients [22].

In contrast, our patients with combined endocrine therapy presented lower AMH-levels than women without adjuvant endocrine treatment. This can be explained by the negative feedback of GnRH analogues on the hypothalamic-pituitary-gonadal axis. Since AMH reflects the pool of antral follicles, GnRH analogues have a direct impact on AMH.

The major limitation of our study is an incomplete capture of menstrual history, which was only surveyed at follow-up time points every three months by a dichotomous question concerning amenorrhea “yes” or “no”. We also lack information regarding pre- and post-treatment pregnancy rate, lifestyle factors like smoking, infertility issues and outcome, or previous use of oral contraceptives. Furthermore, there was no detailed information on preexisting ovarian issues like polycystic ovarian syndrome, which per se presents with higher basal AMH-levels [27]. The strength of this analysis is the large sample size of 170 patients recruited into a multicenter study. The patient cohort is homogeneous with respect to oncologic disease and chemotherapy treatment. Our patients were monitored for a follow-up period of 2 years after chemotherapy, demonstrating a very strong point of our analysis.

We found that the majority of patients show impaired ovarian reserve according to low AMH-levels two years after chemotherapy. Whether low serum AMH concentrations during follow-up have implications on fertility still needs to be investigated. There is a lack of studies examining, if lower AMH-levels after treatment are linked to poor fertility outcome. To conserve young patient's fertility over breast cancer treatment is a task of interdisciplinary cooperation of gynecologists, oncologists and endocrinologists. Therefore, current guidelines suggest counseling our patients about risks and benefits of cryopreservation strategies and suggest embryo- or oocyte freezing harvested by gonadotropin-based stimulation before chemotherapy [24,28].

5. Conclusion

This is a large analysis demonstrating profound interference in ovarian reserve upon AMH-levels of premenopausal breast cancer patients undergoing adjuvant chemotherapy. Thereby age is the most important influencing factors on gonadal function after cytotoxic treatment.

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Conflict of interest statement

E. K. Trapp, J. Steidl, M. S. Kupka, U. Andergassen, A. Kurt, T. Vilsmaier, A. de Gregorio, N. de Gregorio, M. Tzschaschel, C. Lato, A. Polasik, H. Tesch, M. W. Beckmann, and A. Schneeweiss declare no conflict of interests.

J.Jückstock, B. Rack, P. A. Fasching, W. Janni and V. Müller declare conflict of interests: Amgen, Celgene, Eisai, Pierre Fabre, Janssen Diagnostics Chugai, Novartis, Pfizer and AstraZeneca.

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