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

Updated analysis

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Background

Premenopausal women undergoing chemotherapy are at risk of premature ovarian failure and long term side-effects caused by premature menopause. However, knowledge about the rate of ovarian failure and potential markers to evaluate the ovarian reserve is limited, especially in the context of modern chemotherapy concepts. Therefore, Anti-Müllerian hormone (AMH) was measured at 3 time points in premenopausal patients of the SUCCESS study.

Materials & Methods

The German SUCCESS trial is a multicenter phase III study comparing FEC-Docetaxel vs. FEC-Docetaxel + Gemcitabine as adjuvant treatment in patients with node positive or high risk node negative primary breast cancer.

Blood samples were taken prior to and 4 weeks after last cycle of adjuvant chemotherapy, as well as after two years of follow up.

We retrospectively identified 170 patients stratified as premenopausal, aged ≤ 40 years at trial entry, who received 3 cycles of FEC (500/100/500mg/m2) q3w followed by 3 cycles of docetaxel (100mg/m2) q3w as one of the most commonly used chemotherapy regimens in Europe.

Serum AMH levels were evaluated in a central laboratory by a manual immunoassay AMH DSL ELISA (Diagnostic Systems Laboratories, Webster, USA).

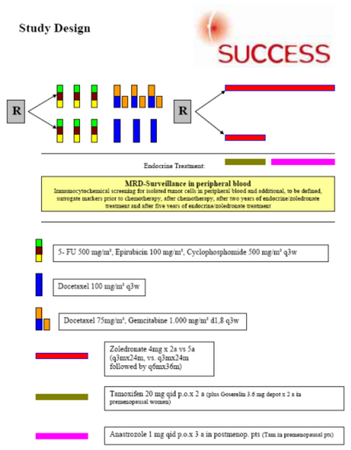

Fig. 1: The SUCCESS study design

Results

Median age within this subgroup was 36 years (21-40 years). 48.8% of the patients had a tumor stage pT1 and 54.7% were node positive. 69.4% were hormone receptor positive and 28.8% Her2 positive (table 1). Median serum AMH level before adjuvant chemotherapy was 1.32 ng/ml (range <0.1-11.3 ng/ml). Immediately after chemotherapy AMH levels dropped in 98.6% of the patients below the threshold of detection (<0.1 ng/ml, range <0.1-0.21 ng/ml). No association to classical prognostic markers, such as tumor stage, lymph node involvement, etc. was observed.

After a follow up period of two years, serum was available from 101 patients. 73.3% of those patients showed no evidence of ovarian function indicated by AMH (<0.1 ng/ml, range <0.1-3.9 ng/ml). AMH levels prior to chemotherapy were significantly correlated with older age, with a reduction of 0.13 ng/ml per life year (p=0.003).12 patients (7.1%) received optional gonadotropin-releasing hormone (GnRH) agonists during chemotherapy. No correlation to AMH-levels two years after cytotoxic treatment could be seen in this small subgroup.

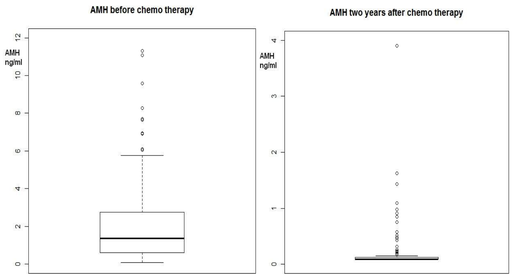

Fig. 2: Serum AMH levels before chemotherapy and after two years

Table 1: Patient characteristics

variable	n (=170)	%
age	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 CTX		
yes	12	7,1%
no	158	92,9%

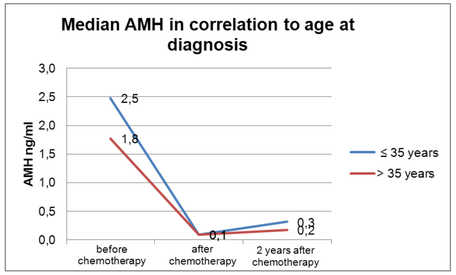

Fig. 3: Median serum AMH in correlation to age at diagnosis

Table 2: Multivariate linear regression analysis

variable	serum AMH 2 years after chemotherapy	
	estimate	p-value
age per life year	-0.011	0.340
serum AMH before chemotherapy	0.090	**< 0.001**
ovarian protection during chemotherapy (GnRH agonists vs. no GnRH agonists)	0.047	0.747
endocrine therapy (tamoxifen vs. none)	-0.186	0.285
endocrine therapy (tamoxifen + goserelin vs. none)	-0.238	**0.011**

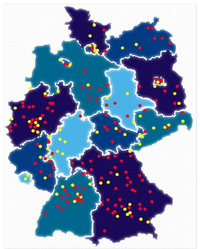

Fig. 4: 251 active SUCCESS study centers in Germany

Conclusion

In this retrospective analysis premenopausal patients showed a high rate of ovarian insufficiency reflected by low serum AMH levels immediately after cytotoxic treatment and after 2 years of follow up. In our cohort, GnRH agonists given as ovarian protectants during chemotherapy do not influence serum AMH two years after chemotherapy. Further data from prospective trials with longer follow up are needed to evaluate the role of serum AMH as a predictor of ovarian failure in breast cancer patients exposed to chemotherapy.

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