Impact of Chemotherapy-induced Ovarian Failure (CIOF) on Disease-free Survival (DFS) and Overall Survival (OS) in Young Women with Early Breast Cancer (EBC)

Jenny Furlanetto[1], Valentina Nekljudova[1], Andreas Schneeweiss[2], Christian Thode[3], Carsten Denkert[4], Michael Untch[5], Martina Bassy[3], Thomas Karn[6], Peter A. Fasching[7], Elmar Stickeler[8], Christian Schem[9], Frederik Marmé[10], Eva-Maria Grischke[11], Marion van Mackelenbergh[12], Dominika Strik[13], Sabine Schmatloch[14], Volkmar Müller[15], Sibylle Loibl[1]

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[1] German Breast Group, Neu-Isenburg, Germany; [2] National Center for Tumor Disease, Germany; [3] Amedes MVZ wagnerstibbe für Laboratoriumsmedizin, medizinische Mikrobiologie und Immunologie, Göttingen, Germany; [4] Institut für Pathologie, Charité Berlin (Institut für Pathologie Philipps-Universität Marburg); [5] Helios Kliniken Berlin-Buch; Germany; [6] Universitätsklinikum Frankfurt, Germany; [7] University Hospital Erlangen, Germany; [8] Uniklinik RWTH Aachen, Germany; [9] Mammazentrum Hamburg, Germany; [10] Universitätsfrauenklinik Mannheim, Germany; [11] Universitätsklinikum Tübingen, Germany; [12] Universitätsklinikum Schleswig-Holstein, Klinik für Gynäkologie und Geburtshilfe, Schleswig-Holstein, Germany; [13] Endokrinologikum Berlin, Germany; [14] Elisabeth Krankenhaus Kassel, Germany; [15] Universitätsklinikum Hamburg-Eppendorf, Germany.

Background

Young patients with BC have a risk of developing premature ovarian failure. The incidence of chemotherapy-induced amenorrhea (CIA) ranges between 45-61% among different studies.[1,2]

We have previously reported that the majority of young women experienced chemotherapy-induced ovarian failure after chemotherapy (CT) for EBC. Age, CT regimen, duration and density influenced the rate of CIOF.[3] Moreover, nearly 70% of women regain premenopausal hormone levels of follicle-stimulating hormone (FSH) and estradiol (E2) within 2 years after end of CT. However, only less than one third maintain their fertility potential as predicted by anti-Müllerian hormone (AMH).[4]

Previous data showed, that CT-induced amenorrhea was associated with a better DFS and OS in premenopausal patients with EBC, regardless of the hormone-receptor status.[5]

Here we report results on the impact of CIOF on DFS and OS in young women with EBC.

Patients and Methods

Overall, 740 patients aged ≤45 years treated with anthracycline/taxane (A/T)-based CT for EBC from 4 German neo-/adjuvant trials were examined. Centrally assessed E2 and FSH in paired blood samples collected at baseline and 4 weeks after the last therapy infusion were considered. CIOF was defined as estradiol <52.2 ng/L and FSH >12.4IU/L after CT for those patients with premenopausal hormone levels at baseline. 696 patients with premenopausal hormone levels at baseline were included in the present analysis.

Objectives:

1. Distribution of E2 and FSH values at end of treatment (EOT)
2. 4-year DFS and OS (rate, hazard ratio (HR) and 95% confidence interval (CI)) overall and in subgroups by hormone-receptor status (positive, negative) and age (<30, 30-34, 35-39, ≥40 years)
3. DFS according to FSH values (10 unit increase in FSH values and quartiles) at EOT.

Results

- Among the 740 examined patients, median age was 40 (range 21-45) years; 57.2% had BMI 18.5-<25, 41.1% ≥25; 32% of the patients had luminal, 35.9% HER2+, 32.0% triple-negative BC; 94.1% (N=696) had premenopausal hormone levels at baseline. Overall, 8.1% of patients received taxane treatment only before EOT; 44.5% of patients received dose-dense CT; CT duration was 24 weeks for 47.4% of the patients, 12 weeks for 8.1% of the patients. Median follow-up was 49.6 months. 4-year DFS and OS rates as well as HR overall and in subgroups are presented in Table 1.
- At EOT E2 levels were under the detectable threshold for most patients (n=395), whereas FSH level were approximately normally distributed (Figure 1). Each 10 unit increase in FSH values was associated with a reduction in the risk of a DFS event by HR_{10unit} =0.91 95%CI [0.87-0.96], p<0.001. Patients with FSH levels at EOT within the first (lower) quartiles (Q), had the worst DFS compared to patients with FSH levels within Q2-4, whereas patients within Q4 (upper) had the better DFS.

Table 1. 4-year DFS and OS rates as well as HR overall and in subgroups

	DFS				OS			
	4-year rate (%)		log rank p-value	HR [95% CI]*	4-year rate (%)		log rank p-value	HR [95% CI]*
	no CIOF	CIOF			no CIOF	CIOF		
overall (n=696)	65.2	84.0	**<0.001**	2.06 [1.36-3.12]	89.5	92.7	0.272	1.46 [0.74-2.90]
hormone-receptor status								
negative (n=301)	71.6	79.6	0.266	1.47 [0.74-2.89]	91.8	88.7	0.729	0.81 [0.25-2.67]
positive (n=395)	61.8	87.5	**<0.001**	2.69 [1.57-4.60]	88.4	95.9	**0.035**	0.49 [1.04-5.99]
age (years)								
<30 (n=60)	68.3	92.6	**0.026**	4.87 [1.05-22.63]	90.3	95.5	0.254	3.48 [0.36-33.99]
30-34 (n=99)	59.9	80.1	0.108	1.99 [0.85-4.68]	96.3	92.1	0.934	0.94 [0.19-4.56]
35-39 (n=200)	63.5	81.9	0.116	1.85 [0.85-4.04]	84.9	93.2	0.380	1.75 [0.49-6.23]
≥40 (n=337)	69.3	85.2	0.565	1.41 [0.44-4.51]	86.7	92.4	0.361	1.93 [0.46-8.17]

*HR no CIOF vs CIOF. Abbreviations: CIOF, chemotherapy-induce ovarian failure; HR, Hazard Ratio

Figure 1. Distribution of estradiol (A) and FSH (B) values at the end of treatment

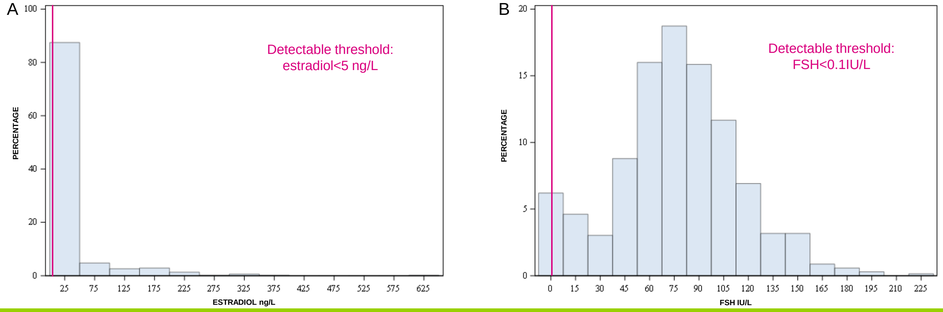
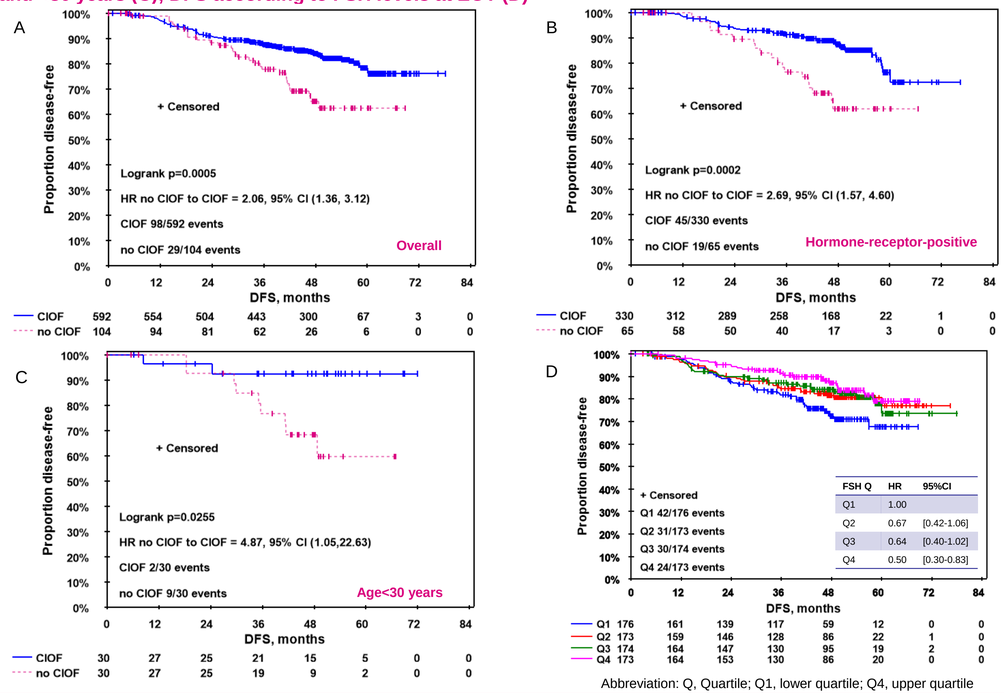


Figure 2. DFS by no CIOF vs CIOF at EOT overall (A), in patients with hormone-receptor-positive status (B) and <30 years (C); DFS according to FSH levels at EOT (D)



Abbreviation: Q, Quartile; Q1, lower quartile; Q4, upper quartile

Conclusions

Patients with CIOF after A/T-based CT for EBC show a better DFS, especially in women with hormone-receptor positive EBC or <30 years. The improvement in DFS seems to translate in an OS advantage in patients with hormone-receptor positive EBC. Patients with the highest levels of FSH at EOT derived a great benefit in DFS compared to patients with lower FSH levels.

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